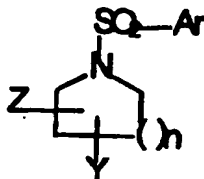




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|---|-----------|---|
| (51) International Patent Classification 6 : C07D 207/48, 211/96, A61K 31/445, 31/40, C07D 417/06, 417/12, 417/14, 403/04, 401/14 | A1 | (11) International Publication Number: WO 98/08814 (43) International Publication Date: 5 March 1998 (05.03.98) |
| (21) International Application Number: PCT/US97/14554 (22) International Filing Date: 22 August 1997 (22.08.97) (30) Priority Data: 60/024,746 28 August 1996 (28.08.96) US (71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US). (72) Inventors: ALMSTEAD, Neil, Gregory; 6348 Trail Ridge Court, Loveland, OH 45140 (US). DE, Biswanath; 11269 Cornell Woods Drive, Cincinnati, OH 45241 (US). BRADLEY, Rimma, Sandler; 60 Westwood Drive #2C, Fairfield, OH 45014 (US). GARRETT, Garry, Steven; 1585 Parliament Court, Fairfield, OH 45014 (US). MARLIN, John, Emory, II; 6907 Driftwood Lane, Cincinnati, OH 45241 (US). MCIVER, John, McMillan; 832 Cedarhill Drive, Cincinnati, OH 45240 (US). WANG, Zhe; 2106-C Haven Road, Wilmington, DE 19809 (US). TAIWO, Yetunde, Olabisi; 7398 Coachford Drive, West Chester, OH 45069 (US). | | (74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. |

(54) Title: BIDENTATE METALLOPROTEASE INHIBITORS



(I)

(57) Abstract

The invention provides compounds which are useful as inhibitors of metalloproteases, and which are effective in treating conditions characterized by excess activity of these enzymes. In particular, the present invention relates to a compound having a structure according to Formula (I) as described in the claims, or an optical isomer, diastereomer or enantiomer thereof, or a pharmaceutically-acceptable salt, or biohydrolyzable alkoxyamide, ester, acyloxyamide, or imide thereof. Also disclosed are compounds, pharmaceutical compositions and methods of treating diseases characterized by metalloprotease activity using these compounds or the pharmaceutical compositions containing them.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | ML | Mali | TR | Turkey |
| BG | Bulgaria | HU | Hungary | MN | Mongolia | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MR | Mauritania | UA | Ukraine |
| BR | Brazil | IL | Israel | MW | Malawi | UG | Uganda |
| BY | Belarus | IS | Iceland | MX | Mexico | US | United States of America |
| CA | Canada | IT | Italy | NE | Niger | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NL | Netherlands | VN | Viet Nam |
| CG | Congo | KE | Kenya | NO | Norway | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NZ | New Zealand | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | PL | Poland | | |
| CM | Cameroon | KR | Republic of Korea | PT | Portugal | | |
| CN | China | KZ | Kazakhstan | RO | Romania | | |
| CU | Cuba | LC | Saint Lucia | RU | Russian Federation | | |
| CZ | Czech Republic | LI | Liechtenstein | SD | Sudan | | |
| DE | Germany | LK | Sri Lanka | SE | Sweden | | |
| DK | Denmark | LR | Liberia | SG | Singapore | | |
| EE | Estonia | | | | | | |

BIDENTATE METALLOPROTEASE INHIBITORS

CROSS REFERENCE

TECHNICAL FIELD

This invention is directed to compounds which are useful in treating diseases, disorders and conditions associated with unwanted metalloprotease activity.

BACKGROUND

A number of structurally related metalloproteases [MPs] effect the breakdown of structural proteins. These metalloproteases often act on the intercellular matrix, and thus are involved in tissue breakdown and remodeling. Such proteins are referred to as metalloproteases or MPs. There are several different families of MPs, classified by sequence homology. Several families of known MPs, as well as examples thereof, are disclosed in the art.

These MPs include Matrix-Metallo Proteases [MMPs], zinc metalloproteases, many of the membrane bound metalloproteases, TNF converting enzymes, angiotensin-converting enzymes (ACEs), disintegrins, including ADAMs (See Wolfsberg et al, 131 *J. Cell Bio.* 275-78 October, 1995), and the enkephalinases. Examples of MPs include human skin fibroblast collagenase, human skin fibroblast gelatinase, human sputum collagenase, aggrecanase and gelatinase, and human stromelysin. Collagenase, stromelysin, aggrecanase and related enzymes are thought to be important in mediating the symptomatology of a number of diseases.

Potential therapeutic indications of MP inhibitors have been discussed in the literature. See for example, U.S. Patent 5,506,242 (Ciba Geigy Corp.); U.S. Patent 5,403,952 (Merck & Co.); PCT published application WO 96/06074 (British Bio Tech Ltd); PCT Publication WO 96/00214 (Ciba Geigy); WO 95/35275 (British Bio Tech Ltd); WO 95/35276 (British Bio Tech Ltd); WO 95/33731 (Hoffman-LaRoche); WO 95/33709 (Hoffman-LaRoche); WO 95/32944 (British Bio Tech Ltd); WO 95/26989 (Merck); WO 95/29892 (DuPont Merck); WO 95/24921 (Inst. Opthamology); WO 95/23790 (SmithKline Beecham); WO 95/22966 (Sanofi Winthrop); WO 95/19965 (Glycomed); WO 95 19956 (British Bio Tech Ltd); WO 95/19957 (British Bio Tech Ltd); WO 95/19961 (British Bio Tech Ltd) WO 95/13289 (Chiroscience Ltd.); WO 95/12603 (Syntex); WO 95/09633 (Florida State Univ); WO 95/09620 (Florida State Univ.); WO 95/04033 (Celltech); WO 94/25434 (Celltech); WO 94/25435 (Celltech); WO 93/14112 (Merck); WO 94/0019 (Glaxo); WO 93/21942 (British Bio Tech Ltd); WO 92/22523 (Res. Corp. Tech. Inc.); WO 94/10990 (British Bio Tech Ltd); WO 93/09090 (Yamanouchi); and British patents GB

2282598 (Merck) and GB 2268934 (British Bio Tech Ltd); Published European Patent Applications EP 95/684240 (Hoffman La Roche); EP 574758 (Hoffman LaRoche); EP 575844 (Hoffman LaRoche); Published Japanese applications; JP 08053403 (Fujusowa Pharm. Co. Ltd.); JP 7304770 (Kanebo Ltd.); and Bird et al J. Med Chem vol. 37, pp. 158-69 (1994). Examples of potential therapeutic uses of MP inhibitors include rheumatoid arthritis (Mullins, D. E., et al., Biochim. Biophys. Acta, (1983) 695:117-214); osteoarthritis (Henderson, B., et al., Drugs of the Future (1990) 15:495-508); the metastasis of tumor cells (ibid, Broadhurst, M. J., et al., European Patent Application 276,436 (published 1987), Reich, R., et al., 48 Cancer Res. 3307-3312 (1988); and various ulcerations or ulcerative conditions of tissue. For example, ulcerative conditions can result in the cornea as the result of alkali burns or as a result of infection by *Pseudomonas aeruginosa*, *Acanthamoeba*, Herpes simplex and vaccinia viruses.

Other examples of conditions characterized by undesired metalloprotease activity include periodontal disease, epidermolysis bullosa, fever, inflammation and scleritis (Cf. DeCicco et al, WO 95 29892 published November 9, 1995).

In view of the involvement of such metalloproteases in a number of disease conditions, attempts have been made to prepare inhibitors to these enzymes. A number of such inhibitors are disclosed in the literature. Examples include U.S. Patent No. 5,183,900, issued February 2, 1993 to Galardy; U.S. Patent No. 4,996,358, issued February 26, 1991 to Handa, et al.; U.S. Patent No. 4,771,038, issued September 13, 1988 to Wolanin, et al.; U.S. Patent Number 4,743,587, issued May 10, 1988 to Dickens, et al., European Patent Publication Number 575,844, published December 29, 1993 by Broadhurst, et al.; International Patent Publication No. WO 93/09090, published May 13, 1993 by Isomura, et al.; World Patent Publication 92/17460, published October 15, 1992 by Markwell et al.; and European Patent Publication Number 498,665, published August 12, 1992 by Beckett, et al.

Metalloprotease inhibitors are useful in treating diseases caused, at least in part, by breakdown of structural proteins. Though a variety of inhibitors have been prepared, there is a continuing need for potent metalloprotease inhibitors useful in treating such diseases. Applicants have found that the compounds of the present invention are potent metalloprotease inhibitors.

OBJECTS OF THE INVENTION

Thus it is an object of the present invention to provide compounds useful for the treatment of conditions and diseases which are characterized by unwanted MP activity.

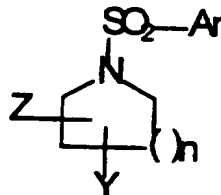
It is also an object of the invention to provide potent inhibitors of metalloproteases.

It is a further object of the invention to provide pharmaceutical compositions comprising such inhibitors.

It is also an object of the invention to provide a method of treatment for metalloprotease related maladies.

SUMMARY OF THE INVENTION

The invention provides compounds which are useful as inhibitors of metalloproteases, and which are effective in treating conditions characterized by excess activity of these enzymes. In particular, the present invention relates to a compound having a structure according to Formula (I)



(I)

wherein

n is an integer from 1 to 3, and 0 to 2 additional heteroatoms, chosen from O, N, or S may occur in the backbone of the ring in the place of carbon, and where S occurs it may be in the form S, SO, or SO₂ and where N occurs it is in the form NR₅ and R₅ is chosen from hydrogen, alkyl, heteroalkyl, heteroaryl, aryl, SO₂R₁₀, COR₁₁, CSR₁₂, PO(R₁₃)₂;

Z is independently one or more of (CH₂)_m(CR₁R₂)_oSR₃; and

R₁ is independently hydrogen, alkyl, CH₂SR₃ or CH₂C(W)R₄, and R₄ is alkoxy, hydroxy, NR₅, alkylthio, or thio; and R₅ is independently one or more of heterocyclalkyl, alkyl, aryl, heteroalkyl, heteraryl, hydrogen or may with W form a heterocyclic ring;

R₂ is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylene, aryl or heteroaryl,

W is O or S,

R₃ is hydrogen, alkyl, aryl, heteroaryl;

and m and o are integers, independently chosen from 0, 1 and 2;

Y is independently one or more of hydrogen, hydroxy, oxo, a spiro moiety, SOR₆, SO₂R₁₀, alkoxy, aryloxy, alkyl aryl, heteroaryl, COR₁₁, CSR₁₂, amino, wherein amino is of formula NR₈R₉, wherein R₈ and R₉ are independently chosen from hydrogen, alkyl, heteroalkyl, heteroaryl, aryl, OR₃, SO₂R₁₀, COR₁₁, CSR₁₂, PO(R₁₃)₂; and

R₆ is alkyl, aryl, heteroaryl;

R₁₀ is alkyl, aryl, heteroaryl, heteroalkyl, amino, alkylamino, dialkylamino, arylamino, diarylamino and alkylaryl amino;

R₁₁ is hydrogen, alkoxy, aryloxy, heteroaryloxy, alkyl, aryl, heteroaryl, heteroalkyl, amino, alkylamino, dialkylamino, arylamino and alkylaryl amino;

R₁₂ is alkyl, aryl, heteroaryl, heteroalkyl, amino, alkylamino, dialkylamino, arylamino, diarylamino and alkylaryl amino;

R₁₃ is alkyl, aryl, heteroaryl, heteroalkyl;

Ar is substituted or unsubstituted; alkyl, aryl, carbocyclyl, heterocyclyl, or heteroaryl;

This structure also includes an optical isomer, diastereomer or enantiomer for Formula (I), or a pharmaceutically-acceptable salt, or biohydrolyzable alkoxyamide, ester, acyloxyamide, or imide thereof.

These compounds have the ability to inhibit at least one mammalian matrix metalloprotease. Accordingly, in other aspects, the invention is directed to pharmaceutical compositions containing the compounds of Formula (I), and to methods of treating diseases characterized by metalloprotease activity using these compounds or the pharmaceutical compositions containing them.

Metalloproteases active at a particularly undesired location (e.g., an organ or certain types of cells) can be targeted by conjugating the compounds of the invention to a targeting ligand specific for a marker at that location such as an antibody or fragment thereof or a receptor ligand. Conjugation methods are known in the art.

The invention is also directed to various other processes which take advantage of the unique properties of these compounds. Thus, in another aspect, the invention is directed to the compounds of Formula (I) conjugated to solid supports. These conjugates can be used as affinity reagents for the purification of a desired metalloprotease.

In another aspect, the invention is directed to the compounds of Formula (I) conjugated to label. As the compounds of the invention bind to at least one metalloprotease, the label can be used to detect the presence of relatively high levels of metalloprotease in vivo or in vitro cell culture.

In addition, the compounds of Formula (I) can be conjugated to carriers which permit the use of these compounds in immunization protocols to prepare antibodies specifically immunoreactive with the compounds of the invention. Typical conjugation methods are known in the art. These antibodies are then useful both in therapy and in monitoring the dosage of the inhibitors.

DETAILED DESCRIPTION

The compounds of the present invention are inhibitors of mammalian metalloproteases. Preferably, the compounds are those of Formula (I) or a pharmaceutically-acceptable salt, or biohydrolyzable alkoxyamide, acyloxyamide, or imide thereof.

Definitions and Usage of Terms:

The following is a list of definitions for terms used herein.

"Acyl" or "carbonyl" is described as a radical which could be formed by removal of the hydroxy from a carboxylic acid (i.e., $R-C(=O)-$). Preferred acyl groups include (for example) acetyl, formyl, and propionyl.

"Acyloxy" is an oxy radical having an acyl substituent (i.e., $-O-acyl$); for example, $-O-C(=O)-alkyl$.

"Alkoxyacyl" is an acyl radical ($-C(=O)-$) having an alkoxy substituent (i.e., $-O-R$), for example, $-C(=O)-O-alkyl$. This radical can be referred to as an ester.

"Acylamino" is an amino radical having an acyl substituent (i.e., -N-acyl); for example, -NH-C(=O)-alkyl.

"Alkenyl" is an unsubstituted or substituted hydrocarbon chain radical having 2 to 15 carbon atoms; preferably from 2 to 10 carbon atoms; more preferably from 2 to 8; except where indicated. Alkenyl substituents have at least one olefinic double bond (including, for example, vinyl, allyl and butenyl).

"Alkynyl" is an unsubstituted or substituted hydrocarbon chain radical having 2 to 15 carbon atoms; preferably from 2 to 10 carbon atoms; more preferably from 2 to 8; except where indicated. The chain has at least one carbon-carbon triple bond.

"Alkoxy" is an oxygen radical having a hydrocarbon chain substituent, where the hydrocarbon chain is an alkyl or alkenyl (i.e., -O-alkyl or -O-alkenyl). Preferred alkoxy groups include (for example) methoxy, ethoxy, propoxy and allyloxy.

"Alkoxyalkyl" is an unsubstituted or substituted alkyl moiety substituted with an alkoxy moiety (i.e., -alkyl-O-alkyl). Preferred is where the alkyl has 1 to 6 carbon atoms (more preferably 1 to 3 carbon atoms), and the alkoxy has 1 to 6 carbon atoms (more preferably 1 to 3 carbon atoms).

"Alkyl" is an unsubstituted or substituted saturated hydrocarbon chain radical having 1 to 15 carbon atoms; preferably from 1 to 10 carbon atoms; more preferably 1 to 4; except where indicated. Preferred alkyl groups include (for example) substituted or unsubstituted methyl, ethyl, propyl, isopropyl, and butyl.

As referred to herein, "spiro cycle" or "spiro cyclic" refers to a cyclic moiety sharing a carbon on another ring. Such cyclic moiety may be carbocyclic or heterocyclic in nature. Preferred heteroatoms included in the backbone of the heterocyclic spirocycle include oxygen, nitrogen and sulfur. The spiro cycles may be unsubstituted or substituted. Preferred substituents include oxo, hydroxy, alkyl, cycloalkyl, arylalkyl, alkoxy, amino, heteroalkyl, aryloxy, fused rings (e.g., benzothiole, cycloalkyl, heterocycloalkyl, benzimidizoles, pyridylthiole, etc., which may also be substituted) and the like. In addition, the heteroatom of the heterocycle may be substituted if valence allows. Preferred spirocyclic ring sizes include 3-7 membered rings.

Alkylene refers to an alkyl, alkenyl or alkynyl which is diradical, rather than a radical. "Hetero alkylene" is likewise defined as a (diradical) alkylene having a heteroatom in its chain.

"Alkylamino" is an amino radical having one (secondary amine) or two (tertiary amine) alkyl substituents (i.e., -N-alkyl). For example, methylamino (-NHCH₃), dimethylamino (-N(CH₃)₂), methylethylamino (-N(CH₃)CH₂CH₃).

"Aminoacyl" is acyl radical having an amino substituent (i.e., -C(=O)-N); for example, -C(=O)-NH₂. The amino group of the aminoacyl moiety may be unsubstituted (i.e., primary amine) or may be substituted with one (secondary amine) or two (i.e., tertiary amine) alkyl groups.

"Aryl" is an aromatic carbocyclic ring radical. Preferred aryl groups include (for example) phenyl, tolyl, xylyl, cumenyl, naphthyl, biphenyl and fluorenyl. Such groups may be substituted or unsubstituted.

"Arylalkyl" is an alkyl radical substituted with an aryl group. Preferred arylalkyl groups include benzyl, phenylethyl, and phenylpropyl. Such groups may be substituted or unsubstituted.

"Arylalkylamino" is an amine radical substituted with an arylalkyl group (e.g., -NH-benzyl). Such groups may be substituted or unsubstituted.

"Arylamino" is an amine radical substituted with an aryl group (i.e., -NH-aryl). Such groups may be substituted or unsubstituted.

"Aryloxy" is an oxygen radical having an aryl substituent (i.e., -O-aryl). Such groups may be substituted or unsubstituted.

"Carbocyclic ring" is an unsubstituted or substituted, saturated, unsaturated or aromatic, hydrocarbon ring radical. Carbocyclic rings are monocyclic or are fused, bridged or spiro polycyclic ring systems. Monocyclic carbocyclic rings generally contain 4 to 9 atoms, preferably 4 to 7 atoms. Polycyclic carbocyclic rings contain 7 to 17 atoms, preferably from 7 to 12 atoms. Preferred polycyclic systems comprise 4-, 5-, 6- or 7-membered rings fused to 5-, 6-, or 7-membered rings.

"Carbocycle-alkyl" is an unsubstituted or substituted alkyl radical substituted with a carbocyclic ring. Unless otherwise specified, the carbocyclic ring is preferably an aryl or cycloalkyl; more preferably an aryl. Preferred carbocycle-alkyl groups include benzyl, phenylethyl and phenylpropyl.

"Carbocycle-heteroalkyl" is an unsubstituted or substituted heteroalkyl radical substituted with a carbocyclic ring. Unless otherwise specified, the carbocyclic ring is preferably an aryl or cycloalkyl; more preferably an aryl. The heteroalkyl is preferably 2-oxa-propyl, 2-oxa-ethyl, 2-thia-propyl, or 2-thia-ethyl.

"Carboxyalkyl" is an unsubstituted or substituted alkyl radical substituted with a carboxy (-C(=O)OH) moiety. For example, -CH₂-C(=O)OH.

"Cycloalkyl" is a saturated carbocyclic ring radical. Preferred cycloalkyl groups include (for example) cyclopropyl, cyclobutyl and cyclohexyl.

"Cycloheteroalkyl" is a saturated heterocyclic ring. Preferred cycloheteroalkyl groups include (for example) morpholinyl, piperidinyl, piperazinyl, tetrahydrofuryl and hydantoinyl.

"Fused rings" are rings that are superimposed together such that they share two ring atoms. A given ring may be fused to more than one other ring. Fused rings are contemplated in heteroaryl, aryl and heterocycle radicals or the like.

"Heterocycle-alkyl" is an alkyl radical substituted with a heterocyclic ring. The heterocyclic ring is preferably a heteroaryl or cycloheteroalkyl; more preferably a heteroaryl. Preferred

heterocycle alkyl include C₁-C₄ alkyl having preferred heteroaryl appended to them. More preferred is, for example, pyridyl alkyl, and the like.

"Heterocycle-heteroalkyl" is an unsubstituted or substituted heteroalkyl radical substituted with a heterocyclic ring. The heterocyclic ring is preferably an aryl or cycloheteroalkyl; more preferably an aryl.

"Heteroatom" is a nitrogen, sulfur or oxygen atom. Groups containing one or more heteroatoms may contain different heteroatoms.

"Heteroalkenyl" is an unsubstituted or substituted unsaturated chain radical having 3 to 8 members comprising carbon atoms and one or two heteroatoms. The chain has at least one carbon-carbon double bond.

"Heteroalkyl" is an unsubstituted or substituted saturated chain radical having 2 to 8 members comprising carbon atoms and one or two heteroatoms.

"Heterocyclic ring" is an unsubstituted or substituted, saturated, unsaturated or aromatic ring radical comprised of carbon atoms and one or more heteroatoms in the ring. Heterocyclic rings are monocyclic or are fused, bridged, spiro or polycyclic ring systems. Monocyclic heterocyclic rings contain 3 to 9 atoms, preferably 4 to 7 atoms. Polycyclic rings contain 7 to 17 atoms, preferably from 7 to 13 atoms.

"Heteroaryl" is an aromatic heterocyclic ring, either monocyclic or bicyclic radical. Preferred heteroaryl groups include (for example) thienyl, furyl, pyrrolyl, pyridinyl, pyrazinyl, thiazolyl, pyrimidinyl, quinolinyl, and tetrazolyl, benzo thiazolyl, benzofuryl, indolyl and the like. Such groups may be substituted or unsubstituted.

"Halo", "halogen", or "halide" is a chloro, bromo, fluoro or iodo atom radical. bromo, chloro and fluoro are preferred halides.

Also, as referred to herein, a "lower" hydrocarbon moiety (e.g., "lower" alkyl) is a hydrocarbon chain comprised of 1 to 6, preferably from 1 to 4, carbon atoms.

Also, as referred to herein, a "lower" hydrocarbon moiety (e.g., "lower" alkyl) is a hydrocarbon chain comprised of 1 to 6, preferably from 1 to 4, carbon atoms.

As used herein the term "parent ring system" or "parent ring" refers to the ring system that forms the core of the structure described in the Summary of the Invention;



This ring system is of from about 5 to about 7 members and many contain from 0-2 additional heteroatoms chosen from O, S, or N, providing for rings such as morpholine, diazepine, piperidine, thiamorpholine,, and the like. The position of the heteroatom is limited by those ring which are known in the art.

A "pharmaceutically-acceptable salt" is a cationic salt formed at any acidic (e.g., carbonyl) group, or an anionic salt formed at any basic (e.g., amino) group. Many such salts are known in the art, as described in World Patent Publication 87/05297, Johnston et al., published September 11, 1987 (incorporated by reference herein). Preferred cationic salts include the alkali metal salts (such as sodium and potassium), and alkaline earth metal salts (such as magnesium and calcium) and organic salts. Preferred anionic salts include the halides (such as chloride salts).

"Biohydrolyzable alkoxyamide" and "Biohydrolyzable acyloxyamide" are amides of a hydroxamic acid that do not essentially interfere with the inhibitory activity of the compound, or that are readily converted in vivo by a human or lower animal subject to yield an active hydroxamic acid.

A "biohydrolyzable hydroxy imide" is an imide of a Formula (I) compound that does not interfere with the metalloprotease inhibitory activity of these compounds, or that is readily converted in vivo by a human or lower animal subject to yield an active Formula (I) compound. Such hydroxy imides include those that do not interfere with the biological activity of the Formula (I) compounds.

A "biohydrolyzable ester" refers to an ester of a Formula (I) compound that does not interfere with the metalloprotease inhibitory activity of these compounds or that is readily converted by an animal to yield an active Formula (I) compound.

A "solvate" is a complex formed by the combination of a solute (e.g., a hydroxamic acid) and a solvent (e.g., water). See J. Honig et al., The Van Nostrand Chemist's Dictionary, p. 650 (1953). Pharmaceutically-acceptable solvents used according to this invention include those that do not interfere with the biological activity of the hydroxamic acid (e.g., water, ethanol, acetic acid, N,N-dimethylformamide and others known or readily determined by the skilled artisan).

"Optical isomer", "stereoisomer", "diastereomer" as referred to herein have the standard art recognized meanings (Cf., Hawley's Condensed Chemical Dictionary, 11th Ed.).

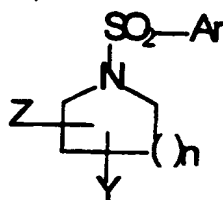
The illustration of specific protected forms and other derivatives of the Formula (I) compounds is not intended to be limiting. The application of other useful protecting groups, salt forms, etc. is within the ability of the skilled artisan.

As defined above and as used herein, substituent groups may themselves be substituted. Such substitution may be with one or more substituents. Such substituents include those listed in C. Hansch and A. Leo, Substituent Constants for Correlation Analysis in Chemistry and Biology (1979), incorporated by reference herein. Preferred substituents include (for example) alkyl, alkenyl, alkoxy, hydroxy, oxo, nitro, amino, aminoalkyl (e.g., aminomethyl, etc.), cyano, halo, carboxy, alkoxyacyl (e.g., carboethoxy, etc.), thiol, aryl, cycloalkyl, heteroaryl, heterocycloalkyl (e.g., piperidinyl, morpholinyl, pyrrolidinyl, etc.), imino, thioxo, hydroxyalkyl, aryl, arylalkyl, and combinations thereof.

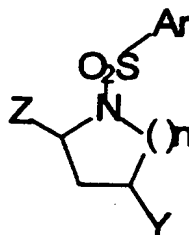
As used herein, "mammalian metalloprotease" means any metal-containing enzyme found in mammalian sources which is capable of catalyzing the breakdown of collagen, gelatin or proteoglycan under suitable assay conditions. Appropriate assay conditions can be found, for example, in U.S. Pat. No. 4,743,587, which references the procedure of Cawston, et al., *Anal Biochem* (1979) 99:340-345, use of a synthetic substrate is described by Weingarten, H., et al., *Biochem. Biophys. Res. Comm.* (1984) 139:1184-1187. Any standard method for analyzing the breakdown of these structural proteins can, of course, be used. The metalloprotease enzymes referred to herein are all zinc-containing proteases which are similar in structure to, for example, human stromelysin or skin fibroblast collagenase. The ability of candidate compounds to inhibit metalloprotease activity can, of course, be tested in the assays described above. Isolated metalloprotease enzymes can be used to confirm the inhibiting activity of the invention compounds, or crude extracts which contain the range of enzymes capable of tissue breakdown can be used.

Compounds:

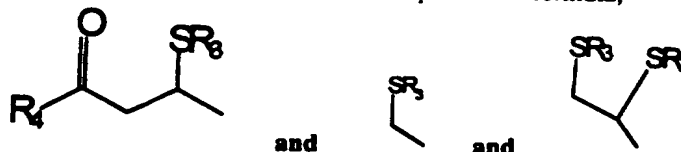
Compounds of the invention include,



as described in the Summary of the Invention, above. One class of preferred compounds are of formula;

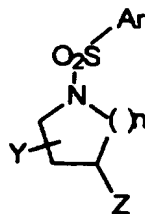


as described above. Of this class, preferred Z includes compounds of formula;



Preferably R_3 is hydrogen and n is 1 or 2. Where R_4 appears, preferably R_4 is alkoxy.

Another preferred class of compounds include those of formula

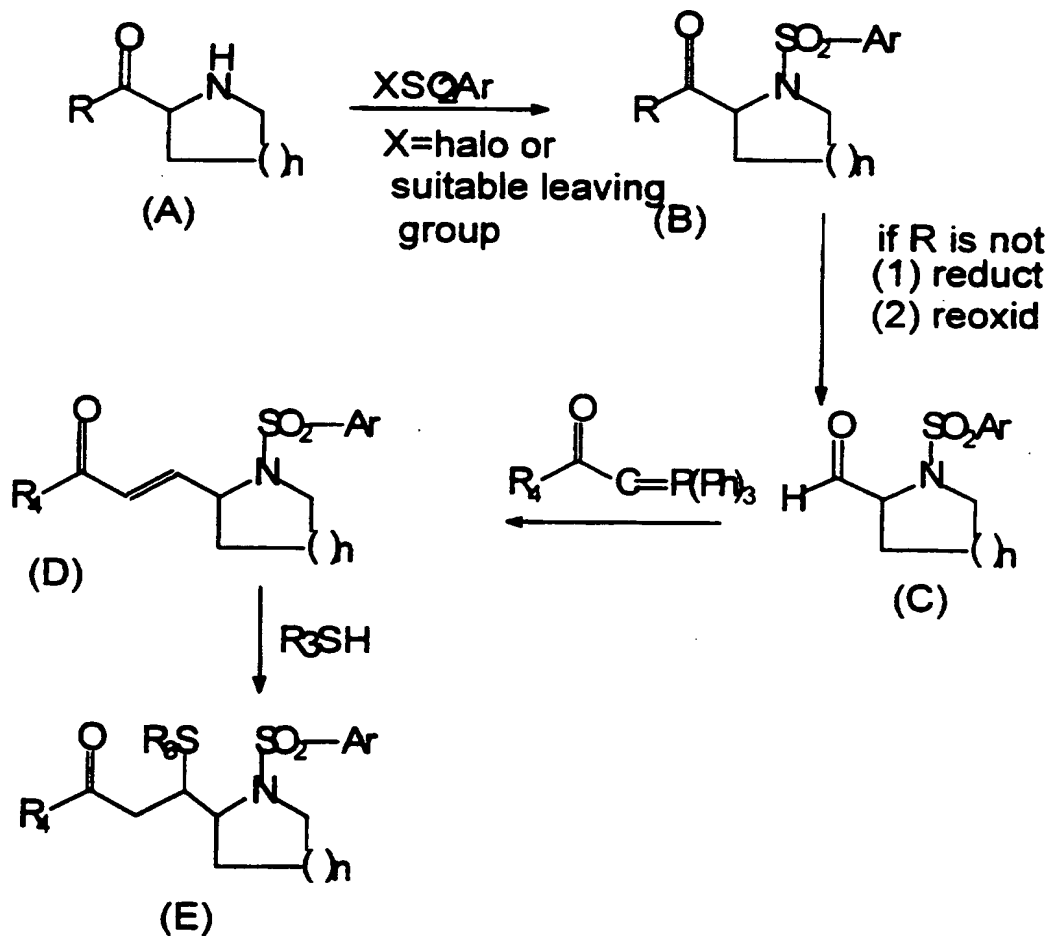


Where Z is SR_3

More preferred compounds have two Z moieties at the preferred positions shown above.

Compound Preparation:

The compounds of Formula (I) can be prepared using a variety of procedures. For clarity, Y is not shown. A preferred method of making the compounds of formula I is illustrated by the scheme below;



Ph=phenyl

SCHEME I

Of course, one of the examples of a Z moiety is exemplified here, but others may be made using known methodologies. It is preferred that the thiol moiety is introduced later in the synthesis for reasons that are apparent to the skilled artisan.

In the scheme above, preferably a piperidine, azepine, diazepine, proline or like compound (A) is converted to the sulfonamide by standard methods to produce (B) which may optionally be converted to an aldehyde (C) and transformed to the α - β unsaturated carbonyl compound (D). This unsaturated compound is thiolated using standard methods to produce a compound of Formula I (E).

Of course, Y may be present in (A), masked in (A) or introduced at the appropriate time during synthesis. The order of synthesis, reagents used and methodologies employed may be varied or may deviate from the scheme above.

For example Y can be introduced via a derivatizable group which can be manipulated or substituted. Such compounds are known or are prepared by known methods. For example, when R is OH, and n is 1, hydroxyproline (A) is converted to its analogous sulfonamide and the hydroxyl is then manipulated to give (B) during this or a subsequent step Y can be added or altered. It is expected that the skilled artisan will employ protecting groups or any other moieties the skilled artisan prefers, provided that ultimately the method provides the compounds of the invention. A variety of compounds can be generated in a similar fashion, using the guidance of the scheme above.

It is recognized that it is preferable to use a protecting group for any reactive functionality such as a carboxyl, hydroxyl and the like, during the formation of the sulfonamide. This is standard practice, well within the normal practice of the skilled artisan. For example, in the above schemes, alkoxy or alkylthio, yield the corresponding hydroxy or thiol compounds by using a standard dealkylating procedure (Bhatt, et al., "Cleavage of Ethers", *Synthesis*, 1983, pp. 249-281).

PREPARATION OF THE Y MOIETY

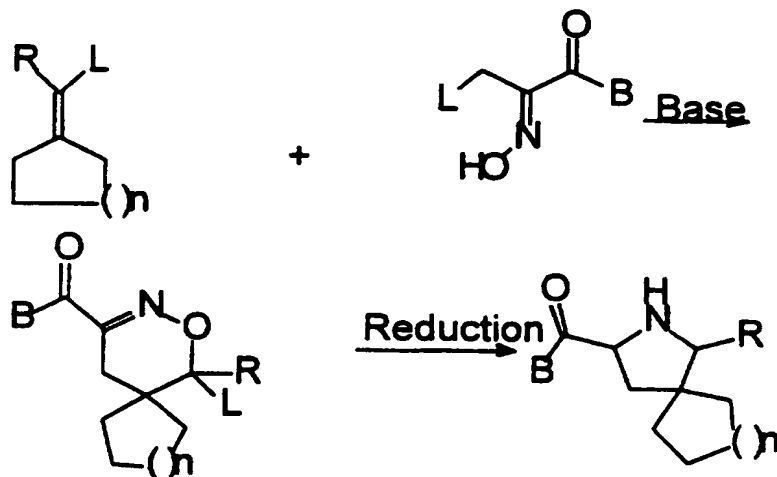
For the manipulation of Y it is understood that the skilled artisan may choose to prepare Y before, after or concurrent with the preparation of Z. It is to be understood that more than one Y and Z may be present in the compounds of formula (I).

A preferred method of introducing Y includes choosing a starting material with a derivatizable group which can be manipulated or substituted into Y. Such compounds are known or are prepared by known methods. Preferred derivatizable groups include hydroxy, alkoxy, oxo, amino, thiol and many others immediately recognizable to the skilled artisan. The skilled artisan will appreciate that judicious choice of starting materials and reactions is essential to preparing any molecules, including those of the invention. For example, where Y is adjacent to the ring nitrogen, a preferred starting material for the preparation of Y includes a lactam, where the derivatizable group is oxo, adjacent to the nitrogen.

Where Y is a ketal or thioketal (including spiroketals) the compounds of the invention may be prepared from the analogous oxo compound using standard protecting group methodologies. Of course, hydroxy, amino, imino, alkoxy, oxo or many other groups can be manipulated into a carbonyl compound.

A preferred method of making the spiro compounds of the invention is via a carbonyl compound, using "protecting group" technology known in the art, such as a thioketal or ketal, and the like. Ketals, acetals and the like are prepared from carbonyl compounds by methods known in the art. Such carbonyl compounds can be made of cyclic hydroxy alkylene amines via oxidation to a ketone, or of lactams, which provide for 2-amino spiro functionality. The order of elaborating the ketal, Z or the sulfonamide may be reordered to optimize yield and avoid undesired reactions.

A preferred method for making compounds of the invention with Y as a carbocycle or a heterocycle which does not employ ketal formation is shown below. In the scheme below Y is depicted as a carbocyclic spirocycle, but one or more heteroatoms may be interspersed in the backbone of the spirocyclic ring. The omission of heteroatoms is meant to add clarity and to aid the reader. It is not meant to limit the claims:



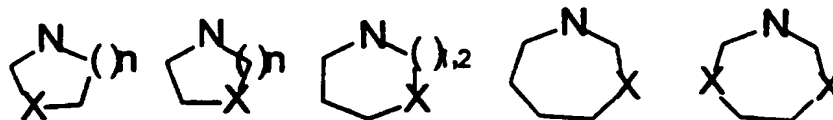
SCHEME II

R is any group that may give rise to Y or to Z. L is a leaving Group. COB is a group that can be manipulated into Z. Of course, one can elaborate Y, Z, the sulfonamide, and any other groups as previously illustrated or as will be apparent to the skilled artisan.

PREPARATION OF HETEROCYCLIC PARENT RING SYSTEMS

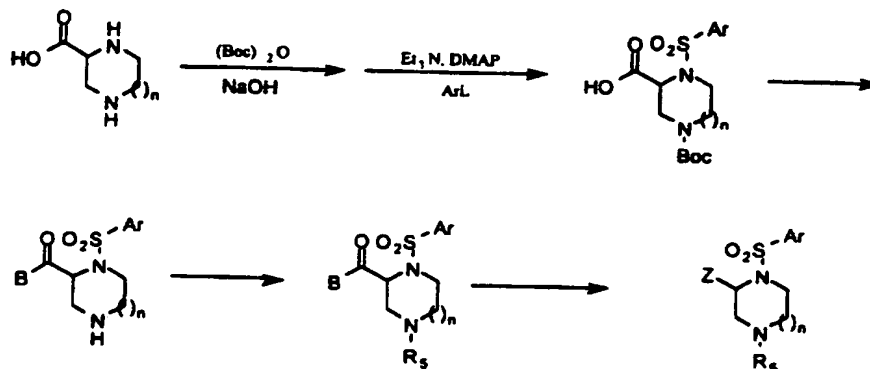
For the preparation and elaboration of the parent ring system as a heterocyclic ring it is understood that the skilled artisan may choose to prepare Y before, after or concurrent with the preparation of the heterocyclic ring. Of course, more than one Y and Z may be present in the compounds of formula (I).

For the purposes of illustration, these parent ring systems include;



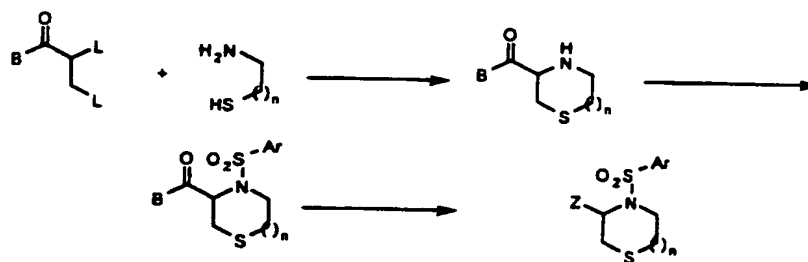
where X is independently chosen from NR_5 , S, SO, SO_2 , or O. Also contemplated in this invention are cyclic sulfonamides and the like.

For compounds where X is NR_5 , the preferred method for the manipulation of R_5 is shown. In the scheme below, L is any acceptable leaving group, and B is a blocking group as above, Boc is an example of a preferred, and art recognized blocking group. The skilled artisan will recognize that the choice of blocking group is within the skill of the artisan working in organic chemistry. Thus the choice of Boc is not required, but preferred.



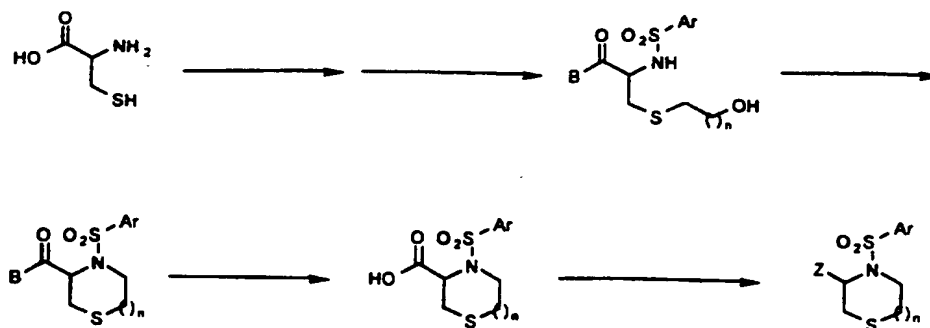
SCHEME III

For compounds containing a sulfur in the heterocyclic ring the preferred methods of ring formation are shown. For the preparation and elaboration of the heterocyclic ring it is understood that the skilled artisan may choose to prepare Y before, after or concurrent with the preparation of the heterocyclic ring.

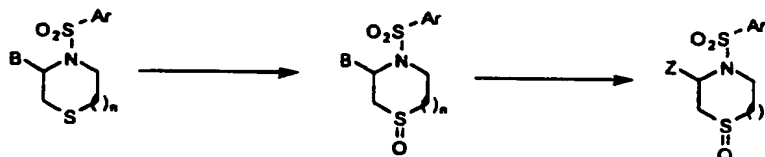


SCHEME IV

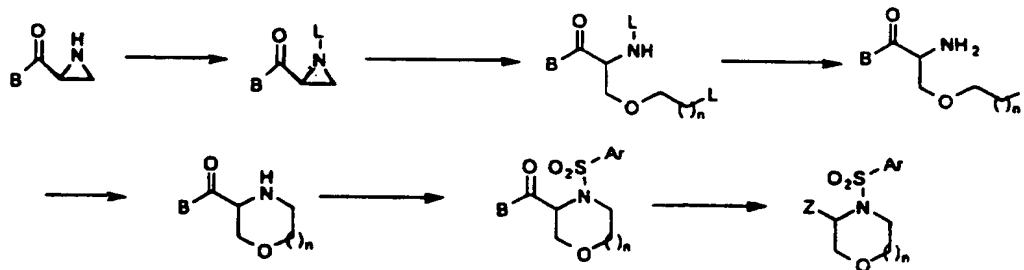
Another acceptable strategy for making the invention having X as sulfur includes the following scheme. The method allows for formation of the sulfonamide and subsequent reaction with a bifunctional moiety. Preferably the OH described in the scheme below is a primary hydroxyl. Closure of the ring uses standard methods. Functionalization and elaboration of the molecule proceeds as described above.

**SCHEME IV**

Where X is sulfur, further elaboration of the heterocyclic ring can be accomplished after the ring has been formed. For example, oxidation of the ring sulfur atom using known methods can provide the corresponding sulfoxides and sulfones as shown. Upon oxidation of the ring sulfur, elaboration of the invention proceeds as described above.

**SCHEME V**

For compounds containing an oxygen in the heterocyclic ring the preferred methods of ring formation are shown. A bifunctional moiety, for example a halo hydroxy species is reacted with an aziridine as shown below. The halo moiety serves as a leaving group, and may be any appropriate leaving group. Upon formation of the ring, elaboration of the invention proceeds as described above.

**SCHEME VI**

PREPARATION OF THE Z MOIETY

Of course the skilled artisan will recognize that some of the schemes applicable to the preparation of Y may be useful in the preparation of Z as noted above. Other preferred methods are provided for the reader. In the above schemes, alkoxy or alkylthio yield the corresponding hydroxy or thiol compounds by using a standard dealkylating procedures (Bhatt, et al., "Cleavage of Ethers", *Synthesis*, 1983, pp. 249-281).

The ordering of steps may be varied to increase yield of desired product. The skilled artisan will also recognize the judicious choice of reactants, solvents, and temperatures is an important component in successful synthesis. While the determination of optimal conditions, etc. is routine, it will be understood that to make a variety of compounds can be generated in a similar fashion, using the guidance of the scheme above.

The starting materials used in preparing the compounds of the invention are known, made by known methods, or are commercially available as a starting material.

It is recognized that the skilled artisan in the art of organic chemistry can readily carry out standard manipulations of organic compounds without further direction; that is, it is well within the scope and practice of the skilled artisan to carry out such manipulations. These include, but are not limited to, reduction of carbonyl compounds to their corresponding alcohols, oxidations, acylations, aromatic substitutions, both electrophilic and nucleophilic, etherifications, esterification and saponification and the like. Examples of these manipulations are discussed in standard texts such as March, Advanced Organic Chemistry (Wiley), Carey and Sundberg, Advanced Organic Chemistry (Vol. 2) and other standard texts.

The skilled artisan will readily appreciate that certain reactions are best carried out when other functionality is masked or protected in the molecule, thus avoiding any undesirable side reactions and/or increasing the yield of the reaction. Often the skilled artisan utilizes protecting groups to accomplish such increased yields or to avoid the undesired reactions. These reactions are found in the literature and are also well within the scope of the skilled artisan. Examples of many of these manipulations can be found for example in T. Greene, Protecting Groups in Organic Synthesis. Of course, amino acids used as starting materials with reactive side chains are preferably blocked to prevent undesired side reactions.

The compounds of the invention may have one or more chiral centers. As a result, one may selectively prepare one optical isomer, including diastereomer and enantiomer, over another, for example by chiral starting materials, catalysts or solvents, or may prepare both stereoisomers or both optical isomers, including diastereomers and enantiomers at once (a racemic mixture). Since the compounds of the invention may exist as racemic mixtures, mixtures of optical isomers, including diastereomers and enantiomers, or stereoisomers may be separated using known methods, such as chiral salts, chiral chromatography and the like.

In addition, it is recognized that one optical isomer, including diastereomer and enantiomer, or stereoisomer may have favorable properties over the other. Thus when disclosing and claiming the invention, when one racemic mixture is disclosed, it is clearly contemplated that both optical isomers, including diastereomers and enantiomers, or stereoisomers substantially free of the other are disclosed and claimed as well.

Methods of use

Metalloproteases (MPs) found in the body operate, in part, by breaking down the extracellular matrix, which comprises extracellular proteins and glycoproteins. These proteins and glycoproteins play

an important role in maintaining the size, shape, structure and stability of tissue in the body. Inhibitors of metalloproteases are useful in treating diseases caused, at least in part, by breakdown of such proteins. It is known that MPs are intimately involved in tissue remodeling. As a result of this activity they have been said to be active in many disorders involving either the:

- breakdown of tissues; including degenerative diseases, such as arthritis, multiple sclerosis and the like; metastasis or mobility of tissues in the body;
- the remodeling of tissues, including fibrotic disease, scarring, benign hyperplasia, and the like.

The compounds of the present invention treat disorders, diseases and/or unwanted conditions which are characterized by unwanted or elevated activity by that class of proteases. For example the compounds can be used to inhibit proteases which

- destroy structural proteins (i.e. the proteins that maintain tissue stability and structure);
- interfere in inter/intracellular signaling, including those implicated in cytokine up-regulation, and/or cytokine processing and/or inflammation, tissue degradation and other maladies [Mohler KM, et al, Nature 370 (1994) 218-220, Gearing AJH, et al, Nature 370 (1994) 555-557 McGeehan GM, et al, Nature 370 (1994) 558-561], and/or
- facilitate processes which are undesired in the subject being treated, for example, the processes of sperm maturation, egg fertilization and the like.

As used herein, a "MP related disorder" or "a MP related disease" is one that involves unwanted or elevated MP activity in the biological manifestation of the disease or disorder; in the biological cascade leading to the disorder; or as a symptom of the disorder. This "involvement" of the MP includes;

- The unwanted or elevated MP activity as a "cause" of the disorder or biological manifestation, whether the activity was elevated genetically, by infection, by autoimmunity, trauma, biomechanical causes, lifestyle [e.g. obesity] or by some other cause;
- The MP as part of the observable manifestation of the disease or disorder. That is, the disease or disorder is measurable in terms of the increased MP activity, or from a clinical standpoint, unwanted or elevated MP levels indicate the disease. MPs need not be the "hallmark" of the disease or disorder;
- The unwanted or elevated MP activity is part of the biochemical or cellular cascade that results or relates to the disease or disorder. In this respect, inhibition of the MP activity interrupts the cascade, and thus controls the disease.

Advantageously, many MPs are not distributed evenly throughout the body. Thus the distribution of MPs expressed in various tissues are often specific to those tissues. For example, the distribution of metalloproteases implicated in the breakdown of tissues in the joints, is not the same as the distribution of metalloproteases found in other tissues. Thus, though not essential for activity or efficacy, certain disorders preferably are treated with compounds that act on specific MPs found in the affected tissues or regions of the body. For example, a compound which displays a higher degree of affinity and

inhibition for a MP found in the joints (e.g. chondrocytes) would be preferred for treatment of disease found there than other compounds which are less specific.

In addition, certain inhibitors are more bioavailable to certain tissues than others, and this judicious choice of inhibitor, with the selectivity described above provides for specific treatment of the disorder, disease or unwanted condition. For example, compounds of this invention vary in their ability to penetrate into the central nervous system. Thus compounds may be selected to produce effects mediated through MPs found specifically outside the central nervous system.

Determination of the specificity of a MP inhibitor of a certain MP is within the skill of the artisan in that field. Appropriate assay conditions can be found in the literature. Specifically assays are known for stromelysin and collagenase. For example, U.S. Pat. No. 4,743,587 references the procedure of Cawston, et al., Anal Biochem (1979) 99:340-345. The use of a synthetic substrate in an assay is described by Weingarten, H., et al., Biochem Biophys Res Comm (1984) 139:1184-1187. Any standard method for analyzing the breakdown of structural proteins by MPs can, of course, be used. The ability of compounds of the invention to inhibit metalloprotease activity can, of course, be tested in the assays found in the literature, or variations thereof. Isolated metalloprotease enzymes can be used to confirm the inhibiting activity of the invention compounds, or crude extracts which contain the range of enzymes capable of tissue breakdown can be used.

As a result of the MP inhibitory effect of the compounds of the invention, the compounds of the invention are also useful in treating the following disorders by virtue of their metalloprotease activity.

The compounds of this invention are also useful for the prophylactic or acute treatment. They are administered in any way the skilled artisan in the fields of medicine or pharmacology would desire. It is immediately apparent to the skilled artisan that preferred routes of administration will depend upon the disease state being treated, and the dosage form chosen. Preferred routes for systemic administration include administration perorally or parenterally.

However, the skilled artisan will readily appreciate the advantage of administering the MP inhibitor directly to the affected area for many disorders. For example, it may be advantageous to administer MP inhibitors directly to the area of the disease or condition as in area affected by surgical trauma (e. g., angioplasty), area affected by scarring or burn (e.g., topical to the skin),

Because the remodeling of bone involves MPs, the compounds of the invention are useful in preventing prosthesis loosening. It is known in the art that over time prostheses loosen, become painful, and may result in further bone injury, thus demanding replacement. The need for replacement of such prostheses includes those such as in, joint replacements (for example hip, knee and shoulder replacements), dental prosthesis, including dentures, bridges and prosthesis secured to the maxilla and/or mandible.

MPs are also active in remodeling of the cardiovascular system (for example, in congestive heart failure). It has been suggested that one of the reasons angioplasty has a higher than expected long term

failure rate (reclosure over time) is that MP activity is not desired or is elevated in response to what may be recognized by the body as "injury" to the basement membrane of the vessel. Thus regulation of MP activity in indications such as dilated cardiomyopathy, congestive heart failure, atherosclerosis, plaque rupture, reperfusion injury, ischemia, chronic obstructive pulmonary disease, angioplasty restenosis and aortic aneurysm may increase long term success of any other treatment, or may be a treatment in itself.

In skin care, MPs are implicated in the remodeling or "turnover" of skin. As a result, the regulation of MPs improves treatment of skin conditions including but not limited to, wrinkle repair, regulation and prevention and repair of ultraviolet induced skin damage. Such a treatment includes prophylactic treatment or treatment before the physiological manifestations are obvious. For example, the MP may be applied as a pre-exposure treatment to prevent ultraviolet damage and/or during or after exposure to prevent or minimize post-exposure damage. In addition, MPs are implicated in skin disorders and diseases related to abnormal tissues that result from abnormal turnover, which includes metalloprotease activity, such as epidermolysis bullosa, psoriasis, scleroderma and atopic dermatitis. The compounds of the invention are also useful for treating the consequences of "normal" injury to the skin including scarring or "contraction" of tissue, for example, following burns. MP inhibition is also useful in surgical procedures involving the skin for prevention of scarring, and promotion of normal tissue growth including in such applications as limb reattachment and refractory surgery (whether by laser or incision).

In addition, MPs are related to disorders involving irregular remodeling of other tissues, such as bone, for example, in otosclerosis and/or osteoporosis, or for specific organs, such as in liver cirrhosis and fibrotic lung disease. Similarly in diseases such as multiple sclerosis, MPs may be involved in the irregular modeling of blood brain barrier and/or myelin sheaths of nervous tissue. Thus regulating MP activity may be used as a strategy in treating, preventing, and controlling such diseases.

MPs are also thought to be involved in many infections, including cytomegalovirus; [CMV] retinitis; HIV, and the resulting syndrome, AIDS.

MPs may also be involved in extra vascularization where surrounding tissue needs to be broken down to allow new blood vessels such as in angiofibroma and hemangioma.

Since MPs break down the extracellular matrix, it is contemplated that inhibitors of these enzymes can be used as birth control agents, for example in preventing ovulation, in preventing penetration of the sperm into and through the extracellular milieu of the ovum, implantation of the fertilized ovum and in preventing sperm maturation.

In addition they are also contemplated to be useful in preventing or stopping premature labor and delivery.

Since MPs are implicated in the inflammatory response, and in the processing of cytokines the compounds are also useful as anti-inflammatories, for use in disease where inflammation is prevalent including, inflammatory bowel disease, Crohn's disease, ulcerative colitis, pancreatitis, diverticulitis, asthma or related lung disease, rheumatoid arthritis, gout and Reiter's Syndrome.

Where autoimmunity is the cause of the disorder, the immune response often triggers MP and cytokine activity. Regulation of MPs in treating such autoimmune disorders is a useful treatment strategy. Thus MP inhibitors can be used for treating disorders including, lupus erythematosus, ankylosing spondylitis, and autoimmune keratitis. Sometimes the side effects of autoimmune therapy result in exacerbation of other conditions mediated by MPs, here MP inhibitor therapy is effective as well, for example, in autoimmune-therapy-induced fibrosis.

In addition, other fibrotic diseases lend themselves to this type of therapy, including pulmonary disease, bronchitis, emphysema, cystic fibrosis, acute respiratory distress syndrome (especially the acute phase response).

Where MPs are implicated in the undesired breakdown of tissue by exogenous agents, these can be treated with MP inhibitors. For example, they are effective as rattlesnake bite antidote, as antivessicants, in treating allergic inflammation, septicemia and shock. In addition, they are useful as antiparasitics (e.g., in malaria) and anti-infectives. For example, they are thought to be useful in treating or preventing viral infection, including infection which would result in herpes, "cold" (e.g., rhinoviral infection), meningitis, hepatitis, HIV infection and AIDS.

MP inhibitors are also thought to be useful in treating Alzheimer's disease, amyotrophic lateral sclerosis (ALS), muscular dystrophy, complications resulting from or arising out of diabetes, especially those involving loss of tissue viability, coagulation, Graft vs. Host disease, leukemia, cachexia, anorexia, proteinuria, and perhaps regulation of hair growth.

For some diseases, conditions or disorders MP inhibition is contemplated to be a preferred method of treatment. Such diseases, conditions or disorders include, arthritis (including osteoarthritis and rheumatoid arthritis), cancer (especially the prevention or arrest of tumor growth and metastasis), ocular disorders (especially corneal ulceration, lack of corneal healing, macular degeneration, and pterygium), and gum disease (especially periodontal disease, and gingivitis).

Compounds preferred for, but not limited to, the treatment of arthritis (including osteoarthritis and rheumatoid arthritis) are those compounds that are selective for the metalloproteases and the disintegrin metalloproteases.

Compounds preferred for, but not limited to, the treatment of cancer (especially the prevention or arrest of tumor growth and metastasis) are those compounds that preferentially inhibit gelatinases or type IV collagenases.

Compounds preferred for, but not limited to, the treatment of ocular disorders (especially corneal ulceration, lack of corneal healing, macular degeneration, and pterygium) are those compounds that broadly inhibit metalloproteases. Preferably these compounds are administered topically, more preferably as a drop or gel.

Compounds preferred for, but not limited to, the treatment of gum disease (especially periodontal disease, and gingivitis) are those compounds that preferentially inhibit collagenases.

Compositions:

The compositions of the invention comprise:

- (a) a safe and effective amount of a compound of Formula (I); and
- (b) a pharmaceutically-acceptable carrier.

As discussed above, numerous diseases are known to be mediated by excess or undesired metalloprotease activity. These include tumor metastasis, osteoarthritis, rheumatoid arthritis, skin inflammation, ulcerations, particularly of the cornea, reaction to infection, periodontitis and the like. Thus, the compounds of the invention are useful in therapy with regard to conditions involving this unwanted activity.

The invention compounds can therefore be formulated into pharmaceutical compositions for use in treatment or prophylaxis of these conditions. Standard pharmaceutical formulation techniques are used, such as those disclosed in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., latest edition.

A "safe and effective amount" of a Formula (I) compound is an amount that is effective, to inhibit metalloproteases at the site(s) of activity, in a mammal subject, without undue adverse side effects (such as toxicity, irritation, or allergic response), commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific "safe and effective amount" will, obviously, vary with such factors as the particular condition being treated, the physical condition of the patient, the duration of treatment, the nature of concurrent therapy (if any), the specific dosage form to be used, the carrier employed, the solubility of the Formula (I) compound therein, and the dosage regimen desired for the composition.

In addition to the subject compound, the compositions of the subject invention contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a mammal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the animal, preferably mammal being treated.

Some examples of substances which can serve as pharmaceutically-acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, live oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and

polyethylene glycol; alginic acid; emulsifiers, such as the TWEENS[®]; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; anti oxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is basically determined by the way the compound is to be administered.

If the subject compound is to be injected, the preferred pharmaceutically-acceptable carrier is sterile, physiological saline, with blood-compatible suspending agent, the pH of which has been adjusted to about 7.4.

In particular, pharmaceutically-acceptable carriers for systemic administration include sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, and pyrogen-free water. Preferred carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil. Preferably, the pharmaceutically-acceptable carrier, in compositions for parenteral administration, comprises at least about 90% by weight of the total composition.

The compositions of this invention are preferably provided in unit dosage form. As used herein, a "unit dosage form" is a composition of this invention containing an amount of a Formula (I) compound that is suitable for administration to a animal, preferably mammal subject, in a single dose, according to good medical practice. These compositions preferably contain from about 5 mg (milligrams) to about 1000 mg, more preferably from about 10 mg to about 500 mg, more preferably from about 10 mg to about 300 mg, of a Formula (I) compound.

The compositions of this invention may be in any of a variety of forms, suitable (for example) for oral, rectal, topical, nasal, ocular or parenteral administration. Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable carriers well-known in the art may be used. These include solid or liquid fillers, diluents, hydrotropes, surface-active agents, and encapsulating substances. Optional pharmaceutically-active materials may be included, which do not substantially interfere with the inhibitory activity of the Formula (I) compound. The amount of carrier employed in conjunction with the Formula (I) compound is sufficient to provide a practical quantity of material for administration per unit dose of the Formula (I) compound. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references, all incorporated by reference herein: Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms 2d Edition (1976).

In addition to the subject compound, the compositions of the subject invention contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein,

means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a animal, preferably mammal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the animal, preferably mammal being treated.

Some examples of substances which can serve as pharmaceutically-acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the TWEENS™; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is basically determined by the way the compound is to be administered.

If the subject compound is to be injected, the preferred pharmaceutically-acceptable carrier is sterile, physiological saline, with blood-compatible suspending agent, the pH of which has been adjusted to about 7.4.

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. These oral forms comprise a safe and effective amount, usually at least about 5%, and preferably from about 25% to about 50%, of the Formula (I) compound. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents.

The pharmaceutically-acceptable carrier suitable for the preparation of unit dosage forms for peroral administration are well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmellose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such

as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the subject invention, and can be readily made by a person skilled in the art.

Peroral compositions also include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, Eudragit[®] coatings, waxes and shellac.

Compositions of the subject invention may optionally include other drug actives.

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

The compositions of this invention can also be administered topically to a subject, e.g., by the direct laying on or spreading of the composition on the epidermal or epithelial tissue of the subject, or transdermally via a "patch". Such compositions include, for example, lotions, creams, solutions, gels and solids. These topical compositions preferably comprise a safe and effective amount, usually at least about 0.1%, and preferably from about 1% to about 5%, of the Formula (I) compound. Suitable carriers for topical administration preferably remain in place on the skin as a continuous film, and resist being removed by perspiration or immersion in water. Generally, the carrier is organic in nature and capable of having dispersed or dissolved therein the Formula (I) compound. The carrier may include pharmaceutically-acceptable emollients, emulsifiers, thickening agents, solvents and the like.

Methods of Administration:

This invention also provides methods of treating or preventing disorders associated with excess or undesired metalloprotease activity in an animal, preferably mammal subject, by administering a safe and effective amount of a Formula (I) compound to said subject. As used herein, a "disorder associated with excess or undesired metalloprotease activity" is any disorder characterized by degradation of proteins. The methods of the invention are useful in treating disorders such as (for example) osteoarthritis, periodontitis, corneal ulceration, tumor invasion, and rheumatoid arthritis.

The Formula (I) compounds and compositions of this invention can be administered topically or systemically. Systemic application includes any method of introducing Formula (I) compound into the tissues of the body, e.g., intra-articular (especially in treatment of rheumatoid arthritis), intrathecal, epidural, intramuscular, transdermal, intravenous, intraperitoneal, subcutaneous, sublingual, rectal, and oral administration. The Formula (I) compounds of the present invention are preferably administered orally.

The specific dosage of inhibitor to be administered, as well as the duration of treatment, and whether the treatment is topical or systemic are interdependent. The dosage and treatment regimen will also depend upon such factors as the specific Formula (I) compound used, the treatment indication, the ability of the Formula (I) compound to reach minimum inhibitory concentrations at the site of the metalloprotease to be inhibited, the personal attributes of the subject (such as weight), compliance with the treatment regimen, and the presence and severity of any side effects of the treatment.

Typically, for a human adult (weighing approximately 70 kilograms), from about 5 mg to about 3000 mg, more preferably from about 5 mg to about 1000 mg, more preferably from about 10 mg to about 100 mg, of Formula (I) compound are administered per day for systemic administration. It is understood that these dosage ranges are by way of example only, and that daily administration can be adjusted depending on the factors listed above.

A preferred method of administration for treatment of rheumatoid arthritis is oral or parenterally via intra-articular injection. As is known and practiced in the art, all formulations for parenteral administration must be sterile. For mammals, especially humans, (assuming an approximate body weight of 70 kilograms) individual doses of from about 10 mg to about 1000 mg are preferred.

A preferred method of systemic administration is oral. Individual doses of from about 10 mg to about 1000 mg, preferably from about 10 mg to about 300 mg are preferred.

Topical administration can be used to deliver the Formula (I) compound systemically, or to treat a subject locally. The amounts of Formula (I) compound to be topically administered depends upon such factors as skin sensitivity, type and location of the tissue to be treated, the composition

and carrier (if any) to be administered, the particular Formula (I) compound to be administered, as well as the particular disorder to be treated and the extent to which systemic (as distinguished from local) effects are desired.

The inhibitors of the invention can be targeted to specific locations where the metalloprotease is accumulated by using targeting ligands. For example, to focus the inhibitors to metalloprotease contained in a tumor, the inhibitor is conjugated to an antibody or fragment thereof which is immunoreactive with a tumor marker as is generally understood in the preparation of immunotoxins in general. The targeting ligand can also be a ligand suitable for a receptor which is present on the tumor. Any targeting ligand which specifically reacts with a marker for the intended target tissue can be used. Methods for coupling the invention compound to the targeting ligand are well known and are similar to those described below for coupling to carrier. The conjugates are formulated and administered as described above.

For localized conditions, topical administration is preferred. For example, to treat ulcerated cornea, direct application to the affected eye may employ a formulation as eyedrops or aerosol. For corneal treatment, the compounds of the invention can also be formulated as gels, drops or ointments, and can be incorporated into collagen or a hydrophilic polymer shield. The materials can also be inserted as a contact lens or reservoir or as a subconjunctival formulation. For treatment of skin inflammation, the compound is applied locally and topically, in a gel, paste, salve or ointment. The mode of treatment thus reflects the nature of the condition and suitable formulations for any selected route are available in the art.

In all of the foregoing, of course, the compounds of the invention can be administered alone or as mixtures, and the compositions may further include additional drugs or excipients as appropriate for the indication.

Some of the compounds of the invention also inhibit bacterial metalloproteases although generally at a lower level than that exhibited with respect to mammalian metalloproteases. Some bacterial metalloproteases seem to be less dependent on the stereochemistry of the inhibitor, whereas substantial differences are found between diastereomers in their ability to inactivate the mammalian proteases. Thus, this pattern of activity can be used to distinguish between the mammalian and bacterial enzymes.

Preparation and Use of Antibodies:

The invention compounds can also be utilized in immunization protocols to obtain antisera immunospecific for the invention compounds. As the invention compounds are relatively small, they are advantageously coupled to antigenically neutral carriers such as the conventionally used keyhole limpet hemocyanin (KLH) or serum albumin carriers. For those invention compounds having a carboxyl functionality, coupling to carrier can be done by methods generally known in the art. For example, the carboxyl residue can be reduced to an aldehyde and coupled to carrier through reaction with sidechain amino groups in protein-based carriers, optionally followed by reduction of imino linkage formed. The carboxyl residue can also be reacted with sidechain amino groups using condensing agents such as dicyclohexyl carbodiimide or other carbodiimide dehydrating agents.

Linker compounds can also be used to effect the coupling; both homobifunctional and heterobifunctional linkers are available from Pierce Chemical Company, Rockford, Ill. The resulting immunogenic complex can then be injected into suitable mammalian subjects such as mice, rabbits, and the like. Suitable protocols involve repeated injection of the immunogen in the presence of adjuvants according to a schedule which boosts production of antibodies in the serum. The titers of the immune serum can readily be measured using immunoassay procedures, now standard in the art, employing the invention compounds as antigens.

The antisera obtained can be used directly or monoclonal antibodies may be obtained by harvesting the peripheral blood lymphocytes or the spleen of the immunized animal and immortalizing the antibody-producing cells, followed by identifying the suitable antibody producers using standard immunoassay techniques.

The polyclonal or monoclonal preparations are then useful in monitoring therapy or prophylaxis regimens involving the compounds of the invention. Suitable samples such as those derived from blood, serum, urine, or saliva can be tested for the presence of the administered inhibitor at various times during the treatment protocol using standard immunoassay techniques which employ the antibody preparations of the invention.

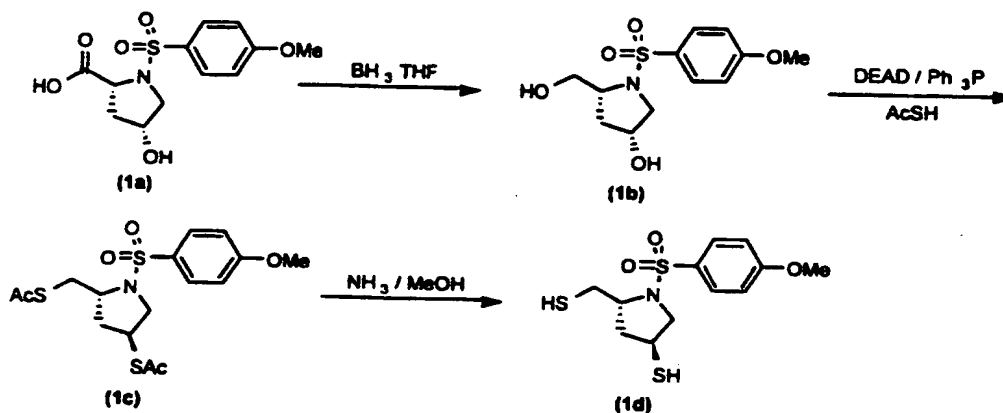
The invention compounds can also be coupled to labels such as scintigraphic labels, e.g., technetium 99 or I-131, using standard coupling methods. The labeled compounds are administered to subjects to determine the locations of excess amounts of one or more metalloproteases in vivo. The ability of the inhibitors to selectively bind metalloprotease is thus taken advantage of to map the distribution of these enzymes in situ. The techniques can also be employed in histological procedures and the labeled invention compounds can be used in competitive immunoassays.

The following non-limiting examples illustrate the compounds, compositions, and uses of the present invention.

Examples

Compounds are analyzed using ^1H and ^{13}C NMR, Elemental analysis, mass spectra and/or IR spectra, as appropriate.

Typically inert solvents are used, preferably in dried form. For example, tetrahydrofuran (THF) is distilled from sodium and benzophenone, diisopropylamine is distilled from calcium hydride and all other solvents are purchased as the appropriate grade. Chromatography is performed on silica gel (70 - 230 mesh; Aldrich) or (230 - 400 mesh; Merck) as appropriate. Thin layer chromatography analysis (TLC) is performed on glass mounted silica gel plates (200 - 300 mesh; Baker) and visualized with UV or 5% phosphomolybdic acid in EtOH.

EXAMPLE 1**Synthesis of 2(R)-Thiomethyl-4-(S)-thio-1-[(4-methoxyphenyl)sulfonyl]pyrrolidine**

1-[(4-Methoxyphenyl)sulfonyl]-cis-4-hydroxy-D-proline (1a): Cis-4-hydroxy-D-proline (9.0 g, 68.6 mmol) is dissolved in 100 mL mixture of water and *p*-dioxane (1:1) and then triethyl amine (19.1 mL, 137.3 mmol), 4-methoxyphenylsulfonyl chloride (15.6 g, 75.5 mmol), and 4-dimethylaminopyridine (0.86 g, 6.86 mmol) are added. The solution is stirred at room temperature overnight. The reaction mixture is washed with sodium bicarbonate and extracted once with ether. The water layer is acidified with 1N HCl until pH ~ 2 is achieved and then the solution is extracted three times with ethyl acetate. The ethyl acetate layers are washed with ammonium chloride, and dried (MgSO_4), filtered and evaporated to give the crude acid. Cl^+ MS: m/z (rel intensity) 302.0 ($\text{M}^+ + \text{H}$, 100).

1-[(4-Methoxyphenyl)sulfonyl]-cis-4-hydroxy-D-prolinol (1b): The acid (0.60 g, 1.99 mmol) is dissolved in 10 mL of anhydrous THF followed by the slow addition of 1.0 M borane-tetrahydrofuran complex (3.98 mL, 3.98 mmol) at room temperature. After stirring for 30 minutes, another 1 mL of the borane-THF complex is added and the solution is stirred for an additional 1.5 hours. The reaction is

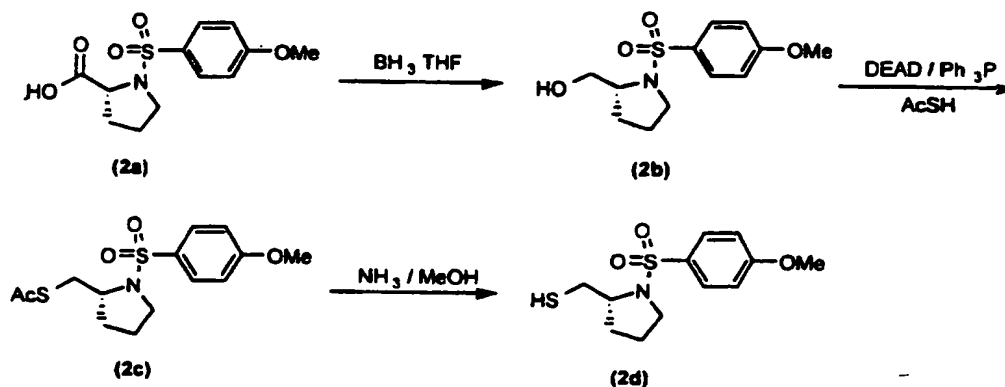
quenched by the slow addition of water and acidified with 1N HCl to pH = 2. The resulting solution is extracted with ethyl acetate three times. The combined organic layers are washed with ammonium chloride, dried (MgSO_4), filtered and evaporated to give the crude product. Cl^+ MS: m/z (rel intensity) 289.0 ($\text{M}^+ + \text{H}$, 100).

2(R)-Acetylthiomethyl-4-(S)-acetylthio-1-[(4-methoxyphenyl)sulfonyl]pyrrolidine (1c): In flask 1, triphenylphosphine (1.09 g, 4.18 mmol) is dissolved in 25 mL of anhydrous THF at -10°C and stirred. The diethyl azodicarboxylate (0.658 mL, 4.18 mmol), is then added and the resulting solution is stirred for 30 minutes. In flask 2, the alcohol (0.300 g, 1.04 mmol) and thiolacetic acid (0.373 mL, 5.22 mmol) are dissolved in 7 mL of anhydrous THF. The contents of flask 2 are cannulated into flask 1. The resulting solution is stirred at 0°C for 4 hours and then at room temperature overnight. The reaction is treated with sodium bicarbonate until pH ~ 9 is achieved and then the solution is extracted three times with ethyl acetate. The organic layers are washed with 1N HCl, sodium bicarbonate, and ammonium chloride, dried (MgSO_4), filtered and evaporated to give a crude solid which is chromatographed on silica gel with hexanes/ ethyl acetate/ methylene chloride (4.5/ 1/ 1) to afford the desired product. Cl^+ MS: m/z (rel intensity) 403.0 ($\text{M}^+ + \text{H}$, 100).

2(R)-Thiomethyl-4-(S)-thio-1-[(4-methoxyphenyl)sulfonyl]pyrrolidine (1d): The dithiol acetate (0.085 g, 0.211 mmol) is dissolved in 10 mL of methanol and the solution is thoroughly degassed. Anhydrous ammonia gas is passed through the solution for 8 minutes and the solution is stirred for 15 minutes. The solution is evaporated down to give the crude product which is chromatographed on silica gel with hexanes/ ethyl acetate/ methylene chloride/ formic acid (70/ 5/ 6/ 0.1) to give the final product as an oil. Cl^+ MS: m/z (rel intensity) 320.0 ($\text{M}^+ + \text{H}$, 100).

EXAMPLE 2

Synthesis of (2R)-2-Thiomethyl-1-[(4-methoxyphenyl)sulfonyl]pyrrolidine

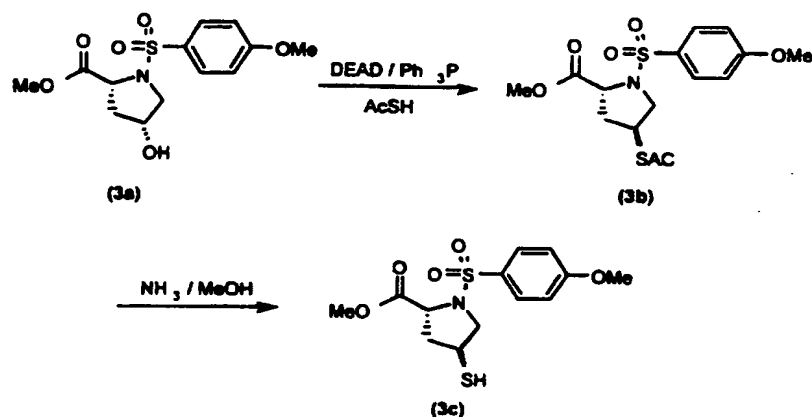


1-[(4-Methoxyphenyl)sulfonyl]-D-proline (2a): D-proline (15 g, 130.3 mmol) is dissolved in a 1:1 mixture of water (150 mL) and *p*-dioxane (150 mL) and then triethyl amine (40 mL, 287 mmol), 4-methoxyphenylsulfonyl chloride (29.0 g, 140.3 mmol), and the 4-dimethylaminopyridine (1.5 g, 13.0 mmol) are added. The solution is stirred at room temperature overnight. The reaction mixture is then treated with 1N HCl until the solution is acidic (pH = 2). The resulting solution is extracted three times with ethyl acetate. The ethyl acetate layers are washed with ammonium chloride, dried (MgSO₄), filtered and evaporated to give the crude compound. Cl^+ MS: *m/z* (rel intensity) ($\text{M}^+ + \text{H}$ 286, 100).

1-[(4-Methoxyphenyl)sulfonyl]-D-prolinol (2b): The acid (5.0 g, 17.5 mmol) is dissolved in 100 mL of anhydrous THF followed by the slow addition of 1.0 M borane-tetrahydrofuran complex (26.5 mL, 26.5 mmol) at room temperature. The reaction mixture is stirred for 2 hours. The reaction is quenched by the slow addition of water and acidified with 1N HCl to pH = 2. The resulting solution is extracted with ethyl acetate 3 times. The organic layers are washed with ammonium chloride, dried (MgSO₄), filtered and evaporated to give the crude product. Cl^+ MS: *m/z* (rel intensity) ($\text{M}^+ + \text{H}$ 272, 100).

2*R*-2-Acetylthiomethyl-1-[(4-methoxyphenyl)sulfonyl]pyrrolidine (2c): In flask 1, triphenylphosphine (0.782 g, 2.98 mmol) is dissolved in 20 mL of anhydrous THF at -10 °C and stirred. The diethyl azodicarboxylate (0.470 mL, 2.98 mmol) is then added and the resulting solution is stirred for 30 minutes. In flask 2, the alcohol (0.404 g, 1.49 mmol) and thiolacetic acid (0.266 mL, 3.73 mmol) are dissolved in 10 mL of anhydrous THF. The contents of flask 2 are cannulated into flask 1. The resulting solution is stirred at 0 °C for 4 hours and then at room temperature overnight. The reaction is treated with sodium bicarbonate until pH ~ 9 is achieved and then the solution is extracted three times with ethyl acetate. The organic layers are washed with 1N HCl, sodium bicarbonate, and ammonium chloride, dried (MgSO₄), filtered and evaporated to give a crude solid. Purification of the solid is accomplished by chromatography on silica gel using ethyl acetate/ methylene chloride (1.5/ 500) as the eluent to afford the desired product. Cl^+ MS: *m/z* (rel intensity) ($\text{M}^+ + \text{H}$ 329.9, 100).

2-Thiomethyl-1-[(4-methoxyphenyl)sulfonyl]pyrrolidine (2d): The thiol acetate (0.110 g, 0.334 mmol) is dissolved in 15 mL of methanol and the solution is thoroughly degassed. Anhydrous ammonia gas is passed through the solution for 8 minutes and the solution stirred for an additional 15 minutes. The solution is evaporated down to give the crude product which is chromatographed on silica gel with hexanes/ ethyl acetate/ methylene chloride (5/ 1/ 1) to provide the final product. Cl^+ MS: *m/z* (rel intensity) ($\text{M}^+ + \text{H}$ 288.0, 100).

EXAMPLE 3**Synthesis of (2*R*,4*S*)-Methyl 4-thio-1-[(4-methoxyphenyl)sulfonyl]proline**

Methyl 1-[(4-methoxyphenyl)sulfonyl]-*cis*-hydroxy-D-proline (3a): 1-[(4-methoxyphenyl)sulfonyl]-*cis*-hydroxy-D-proline (5 g, 16.6 mmol) is dissolved in 150 mL of ether and 20 mL of *p*-dioxane and treated with a 0.7 M solution of diazomethane. The addition is stopped once the color remained yellow. The solution is stirred for an additional hour. The reaction mixture is diluted with 300 mL of ethyl acetate and washed with sodium bicarbonate and ammonium chloride and dried over magnesium sulfate. Cl⁺ MS: *m/z* (rel intensity) 316 (M⁺ + H, 100).

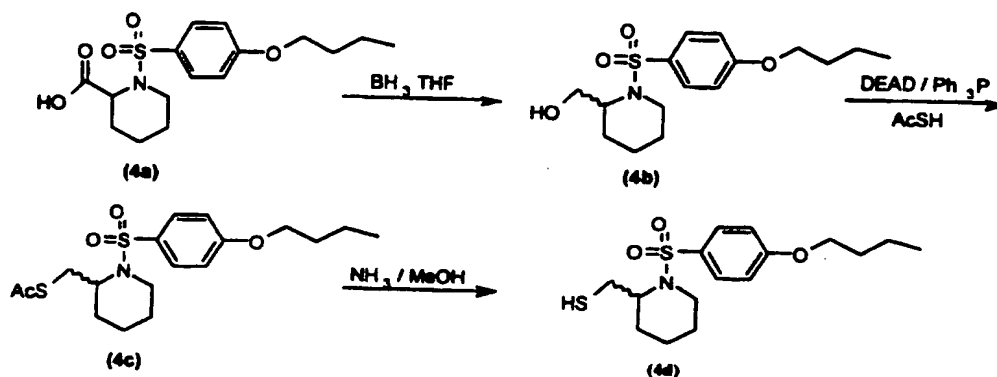
(2*R*,4*S*)-Methyl 4-acetylthio-1-[(4-methoxyphenyl)sulfonyl]proline (3b): In flask 1, triphenylphosphine (5.16 g, 19.68 mmol) is dissolved in 150 mL of anhydrous THF at -10 °C and stirred. The diethyl azodicarboxylate (3.1 mL, 19.68 mmol) is added and the resulting solution is stirred for 30 minutes. In flask 2, the alcohol 1 (3.1 g, 9.84 mmol) and thiolacetic acid (1.76 mL, 24.60 mmol) are dissolved in 30 mL of anhydrous THF. The contents of flask 2 are cannulated into flask 1. The resulting solution is stirred at 0 °C for 4 hours and at room temperature over night. The reaction mixture is treated with sodium bicarbonate and extracted three times with ethyl acetate. The organic layers are washed with 1N HCl, sodium bicarbonate, and ammonium chloride, dried (MgSO₄), filtered and evaporated to give a crude solid which is chromatographed on silica gel with ethyl acetate/ methylene chloride (1/30). Cl⁺ MS: *m/z* (rel intensity) 374 (M⁺ + H, 100).

(2*R*,4*S*)-Methyl 4-thio-1-[(4-methoxyphenyl)sulfonyl]proline (3c): The thiol acetate (0.120 g, 0.321 mmol) is dissolved in 5 mL of methanol and the solution is thoroughly degassed. Anhydrous ammonia gas is passed through the solution for 8 minutes and the solution stirred for an additional 15 minutes. The solution is evaporated down to a crude product which is chromatographed on silica gel with hexanes/ ethyl

acetate/ methylene chloride(4/ 1/ 1) to give the pure product. Cl^+ MS: m/z (rel intensity) 331.9 ($\text{M}^+ + \text{H}$, 100).

EXAMPLE 4

Synthesis of 2(*R,S*)-Thiomethyl-1-[(4-*n*-butoxyphenyl)sulfonyl]piperidine



1-[(4-*n*-Butoxyphenyl)sulfonyl]piperidine-2-carboxylic acid (4a): Pipercolinic acid (0.331 g, 2.56 mmol) is dissolved in 16 mL mixture of water and *p*-dioxane (1:1) followed by the addition of triethyl amine (0.78 mL, 5.64 mmol), 4-butoxyphenylsulfonyl chloride (0.67 g, 2.69 mmol), and 4-dimethylaminopyridine (0.031 g, 0.25 mmol). The resulting solution is stirred at room temperature overnight. The reaction mixture is acidified with 1N HCl and extracted three times with ethyl acetate. The combined organic extracts are washed with ammonium chloride, dried (MgSO_4), filtered and evaporated to give the crude compound. Cl^+ MS: m/z (rel intensity) 342 ($\text{M}^+ + \text{H}$, 100).

2-Hydroxymethyl-1-[(4-*n*-butoxyphenyl)sulfonyl]piperidine (4b): The acid (0.650 g, 1.90 mmol) is dissolved in 15 mL of anhydrous THF followed by the slow addition of 1.0 M borane-tetrahydrofuran complex (3.8 mL, 3.81 mmol) at room temperature. The reaction is stirred for 2 hours and then quenched by the slow addition of water. The resulting solution is acidified with 1N HCl to $\text{pH} = 2$ and extracted with ethyl acetate three times. The organic layers are washed with ammonium chloride, dried (MgSO_4) and evaporated to give the crude product. Cl^+ MS: m/z (rel intensity) 328.1 ($\text{M}^+ + \text{H}$, 100).

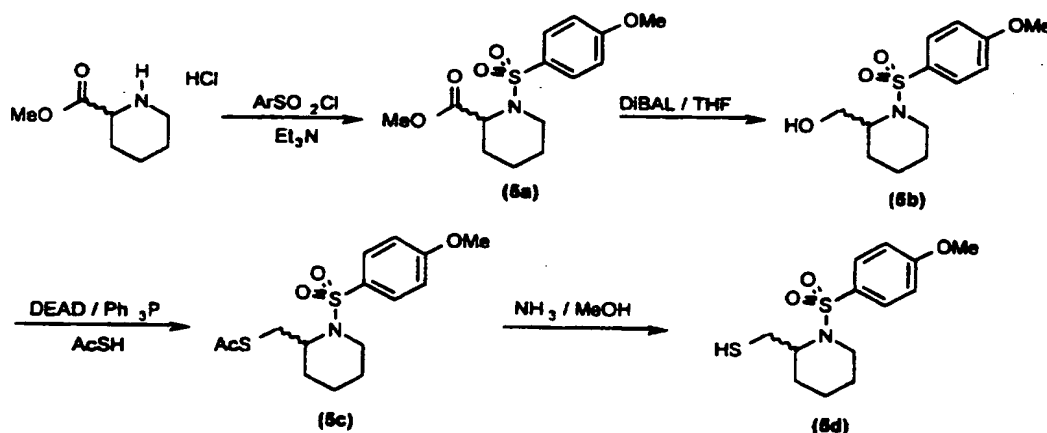
2-Acetylthiomethyl-1-[(4-*n*-butoxyphenyl)sulfonyl]piperidine (4c): In flask 1, triphenylphosphine (0.528 g, 2.01 mmol) is dissolved in 20 mL of anhydrous THF at -10°C and stirred. The diethyl azodicarboxylate (0.317 mL, 2.01 mmol) is then added, and the resulting solution is stirred for 30 minutes. In flask 2, the alcohol (0.325 g, 1.00 mmol) and thiolacetic acid (0.179 mL, 2.51 mmol) are dissolved in 10 mL of anhydrous THF. The contents of flask 2 are cannulated into flask 1. The resulting solution is stirred at 0°C for 4 hours and at room temperature over night. The reaction is treated with sodium

bicarbonate and then extracted three times with ethyl acetate. The organic layers are washed with 1N HCl, sodium bicarbonate, and ammonium chloride, dried (MgSO_4), filtered and evaporated to give a crude solid which is chromatographed on silica gel with hexane /ethyl acetate/ methylene chloride (7 /1 /1). Cl^+ MS: m/z (rel intensity) 386.0 ($\text{M}^+ + \text{H}$, 100).

2(*R,S*)-Thiomethyl-1-[(4-*n*-butoxyphenyl)sulfonyl]piperidine (4d): The thiol acetate (0.105 g, 0.272 mmol) is dissolved in 10 mL of methanol and the solution is thoroughly degassed. Anhydrous ammonia gas is passed through the solution for 8 minutes and the solution stirred for an additional 15 minutes. The solution is evaporated down to give a crude product which is chromatographed on silica gel with hexanes/ ethyl acetate/ methylene chloride(10 / 1/ 1) to afford 0.070 g (75.0%) of a pure product. Cl^+ MS: m/z (rel intensity) 344 ($\text{M}^+ + \text{H}$, 100).

EXAMPLE 5

Synthesis of 2(*R,S*)-Thiomethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine

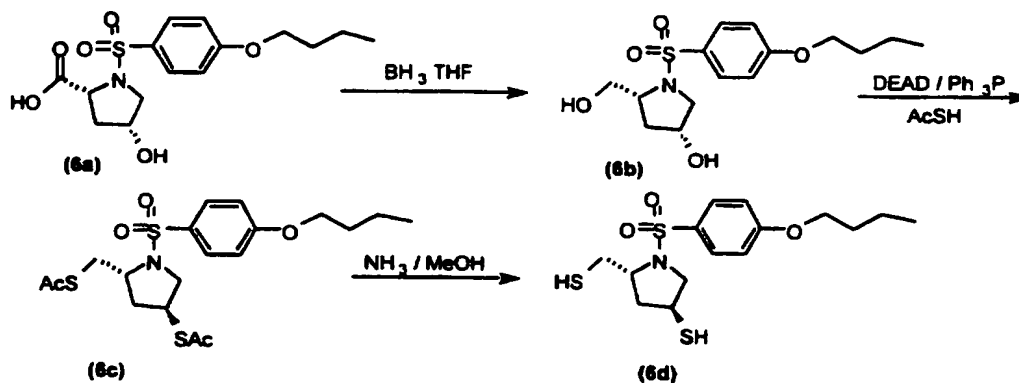


Methyl-1-[(4-methoxyphenyl)sulfonyl]piperidine-2(*R,S*)-carboxylate (5a): Methyl piperidine-2-carboxylate hydrochloride (10.0 g, 55.6 mmol), triethylamine (14.1 g, 19.4 mL, 139.2 mmol, 2.5 equiv), 1,4-dioxane (75 mL), and water (75 mL) are stirred at room temperature and then *p*-methoxyphenylsulfonyl chloride (13.8 g, 66.8 mmol, 1.2 equiv) is added. The resulting solution is stirred at room temperature overnight. The solution is then poured into water and extracted with CH_2Cl_2 . The combined organic extracts are dried (Na_2SO_4) and concentrated to an oil under reduced pressure. Purification of the oil is accomplished by chromatography on silica gel using 7/3 hexane/EtOAc as the eluent. The product is obtained as a colorless oil which solidified upon standing.

2(*R,S*)-1-[(4-Methoxyphenyl)sulfonyl]piperidinemethanol (5b): The sulfonamide (4.0 g, 12.7 mmol) in THF (50 mL) is stirred at room temperature and then diisobutylaluminum hydride in THF (25.5 mL, 25.5 mmol, 2 equiv) is added. The resulting solution is stirred at room temperature for 2 hours and then the reaction mixture is quenched by the addition of water. The solution is extracted with CH₂Cl₂ (3 × 100 mL). The combined organic extracts are dried (Na₂SO₄) and concentrated to an oil under reduced pressure. Purification of the oil is accomplished by chromatography using 1/1 hexane/EtOAc as the eluent. The product is obtained as a clear colorless oil.

2(*R,S*)-Acetylthiomethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine (5c): The alcohol (2.90 g, 10.1 mmol) in CH₂Cl₂ (10 mL) is added to a solution of triphenylphosphine (3.19 g, 12.2 mmol, 1.2 equiv) and diethylazodicarboxylate (1.94 g, 11.1 mmol, 1.1 equiv) in CH₂Cl₂ (20) at -78 °C. The solution is stirred at -78 °C and then the thiolacetic acid (1.55 g, 20.3 mmol, 2.0 equiv) is added. The resulting solution is warmed to room temperature and then stirred for 2 h. The reaction mixture is concentrated to an oil and then silica gel (20 g) is added. The resulting powder is purified by chromatography on silica gel using 7/3 hexane/EtOAc as the eluent to afford the desired thiolacetate as a clear colorless oil. MS (CI, NH₃): 344 (M + H⁺).

2(*R,S*)-Thiomethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine (5d): The thiolacetate 3 (0.295 g, 0.86 mmol) in methanol (20 mL) is stirred under an argon atmosphere at room temperature. The solution is then bubbled with ammonia gas for 20 minutes at room temperature and then the solution is purged with argon gas. The solvent is removed under reduced pressure to leave a colorless oil. Purification of the oil is accomplished by chromatography using 7/3 hexane/EtOAc as the eluent. The product is obtained as a colorless oil. MS (electron spray): 302 (M + H⁺).

EXAMPLE 6**Synthesis of 2(R)-Thiomethyl-4-(S)-thio-1-[(4-n-butoxyphenyl)sulfonyl]pyrrolidine**

1-[(4-Butoxyphenyl)sulfonyl]-cis-4-hydroxy-D-proline (6a): Cis-4-hydroxy-D-proline (0.308 g, 2.67 mmol) is dissolved in 16 mL of a 1:1 mixture of water and *p*-dioxane and then triethyl amine (0.819 mL, 5.89 mmol), 4-butoxyphenylsulfonyl chloride (0.700g, 2.81 mmol), and 4-dimethylaminopyridine (0.033g, 0.268 mmol) are added. The resulting solution is stirred at room temperature overnight. The reaction is then washed with sodium bicarbonate and extracted once with ether. The water layer is acidified with 1N HCl to pH = 2 and extracted three times with ethyl acetate. The ethyl acetate layers are washed with ammonium chloride, dried (MgSO_4), filtered and evaporated to give the crude compound. Cl^+ MS: m/z (rel intensity) 361 ($\text{M}^+ + \text{H}$, 40).

1-[(4-Butoxyphenyl)sulfonyl]-cis-4-hydroxy-D-prolinol (6b): The sulfonamide (0.750 g, 2.18 mmol) is dissolved in 10 mL of anhydrous THF followed by the slow addition of 1.0 M borane-tetrahydrofuran complex (4.4 mL, 4.37 mmol) at room temperature. The solution is stirred for 1.5 hours at room temperature. The reaction is quenched by the slow addition of water, acidified with 1N HCl to pH = 2 and extracted with ethyl acetate three times. The organic layers are washed with ammonium chloride, dried (MgSO_4), filtered and evaporated to give the crude product. Cl^+ MS: m/z (rel intensity) 347.1 ($\text{M}^+ + \text{H}$, 40).

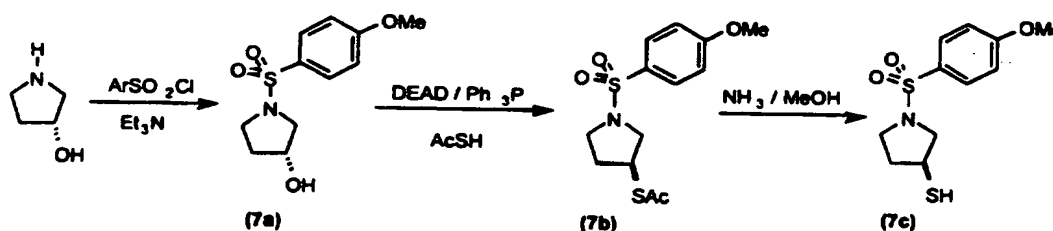
2(R)-Acetylthiomethyl-4-(S)-acetylthio-1-[(4-butoxyphenyl)sulfonyl]pyrrolidine (6c): In flask 1, triphenylphosphine (1.35 g, 5.14 mmol) is dissolved in 25 mL of anhydrous THF at -10°C and stirred. The diethyl azodicarboxylate (0.809 mL, 5.14 mmol) is then added and the resulting solution is stirred for 30 minutes. In flask 2, the alcohol (0.423 g, 1.28 mmol) and thiolacetic acid (0.459 mL, 6.43 mmol) are dissolved in 10 mL of anhydrous THF. The contents of flask 2 are cannulated into flask 1. The resulting solution is stirred at 0°C for 4 hours and then at room temperature overnight. The reaction mixture is

washed with sodium bicarbonate and extracted three times with ethyl acetate. The organic layers are washed with 1N HCl, sodium bicarbonate, and ammonium chloride, dried (MgSO_4), filtered and evaporated to give a crude solid which is chromatographed on silica gel with hexanes/ethyl acetate/methylene chloride (8/1/1). Cl^+ MS: m/z (rel intensity) 446 ($\text{M}^+ + \text{H}$, 100).

2(R)-Thiomethyl-4-(S)-thio-1-[(4-butoxyphenyl)sulfonyl]pyrrolidine (6d): The dithiol acetate (0.150 g, 0.337 mmol) is dissolved in 10 mL of methanol and the solution is thoroughly degassed. Anhydrous ammonia gas is passed through the solution for 8 minutes and the solution stirred for 15 minutes. The solution is evaporated down to the crude product which is chromatographed on silica gel with hexanes/ethyl acetate/methylene chloride/formic acid (10/1/1/0.1) to give the desired product as a pure white solid. Cl^+ MS: m/z (rel intensity) 362 ($\text{M}^+ + \text{H}$, 100).

EXAMPLE 7

Synthesis of 3(R)-Thio-1-[(4-methoxyphenyl)sulfonyl]pyrrolidine



(3S)-3-Hydroxy-1-[(4-methoxyphenyl)sulfonyl]pyrrolidine (7a): The 3(S)-hydroxy-pyrrolidine (1.0 g, 11.5 mmol), triethylamine (2.32 g, 22.9 mmol, 2.0 equiv) in 1,4-dioxane (30 mL) and water (10 mL) is stirred at room temperature and then 4-methoxyphenylsulfonyl chloride (2.61 g, 12.6 mmol, 1.10 equiv) is added. The resulting solution is stirred at room temperature for 3 h. and then the solution is acidified to pH ~1 with 1 N HCl. The solution is poured into water and then extracted with CH_2Cl_2 . The organic extracts are dried (Na_2SO_4) and concentrated to an oil. The oil is purified by chromatography using 1/1 hexane/EtOAc as the eluent to afford 2.62 g (81 %) of the desired product as a colorless oil.

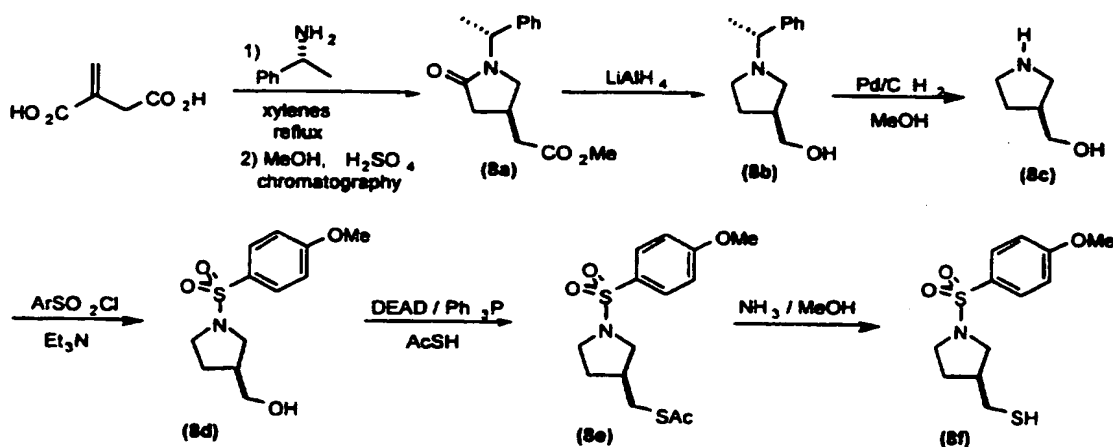
(3R)-3-Acetylthio-1-[(4-methoxyphenyl)sulfonyl]pyrrolidine (7b): The alcohol (1.30 g, 5.05 mmol) in CH_2Cl_2 (30 mL) is added to a solution of triphenylphosphine (1.59 g, 6.06 mmol, 1.2 equiv) and diethylazodicarboxylate (0.97 g, 5.56 mmol, 1.1 equiv) in CH_2Cl_2 (30 mL) at 0 °C. The solution is stirred at 0 °C and then the thiolacetic acid (0.77 g, 10.1 mmol, 2.0 equiv) is added. The resulting solution is warmed to room temperature and then stirred for 2 h. The reaction mixture is concentrated to an oil and

then silica gel (20 g) is added. The resulting powder is purified by chromatography on silica gel using 7/3 hexane/EtOAc as the eluent to afford 1.18 g (74 %) of the desired thiolacetate as a clear colorless oil.

(3R)-3-Thio-1-[(4-methoxyphenyl)sulfonyl]pyrrolidine (7c): The thiolacetate (0.46 g, 1.46 mmol) in methanol (30 mL) and THF (10 mL) is stirred under an argon atmosphere at room temperature. The solution is then bubbled with ammonia gas for 20 minutes at room temperature and then the solution is purged with argon gas. The solvent is removed under reduced pressure to leave a colorless oil. Purification of the oil is accomplished by chromatography using 8/2 hexane/EtOAc as the eluent. The product is obtained as a colorless oil. MS (electron spray): 274 ($M + H^+$).

EXAMPLE 8

Synthesis of 3(S)-Thiomethyl-1-[(4-methoxyphenyl)sulfonyl]pyrrolidine



(1R,3S) Methyl 5-oxo-1-(1-phenylethyl)-3-pyrrolidinecarboxylic acid (8a): Itaconic acid (16.1 g, 124 mmol), (R)-1-phenylethylamine (15.0 g, 124 mmol) and xylenes (150 mL) are heated to reflux for 6 h. Water is removed from the reaction by a Dean-Stark trap. The reaction mixture is cooled to room temperature and then the xylenes are removed under reduced pressure. The product, a white solid, is dissolved in methanol (350 mL) and a catalytic amount of H_2SO_4 is added (0.7 g). The resulting solution is heated to reflux for 18 h. The solvent is removed and the product is purified by chromatography on silica gel (65/35 hexane / EtOAc as eluent) to afford both diastereomers as single entities. The low R_f material is used in the following sequence of reactions.

(1R,3S) 5-oxo-1-(1-phenylethyl)-3-hydroxymethylpyrrolidine (8b): The ester (2.27 g, 9.18 mmol) in THF (50 mL) is stirred at room temperature and then the LiAlH_4 (0.7 g, 18.3 mmol, 2.0 equiv) is slowly

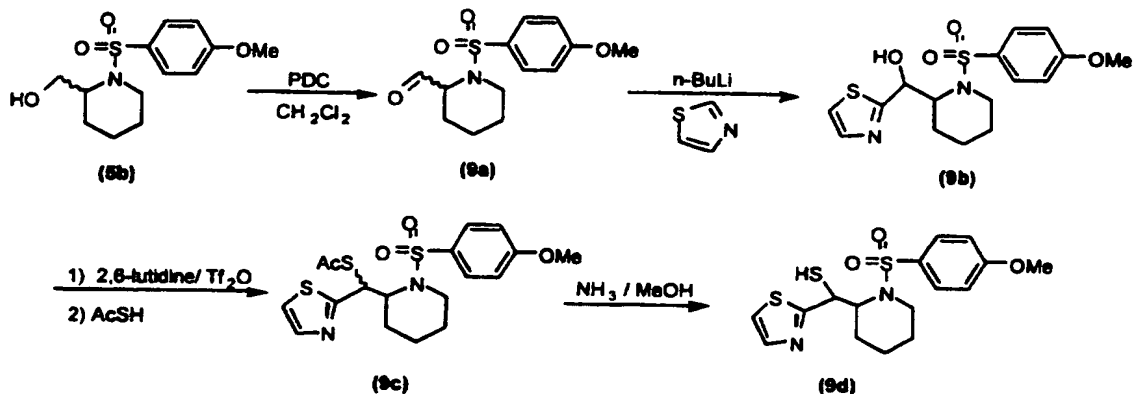
added. After the addition is complete the solution is stirred at reflux for 4 h. The reaction mixture is cooled to room temperature and the EtOAc is slowly added (~ 5 mL). The reaction is quenched by the cautious addition of water (0.7 mL), 15 % NaOH (0.7 mL) and water (3 mL). The solution is stirred at room temperature for 10 minutes and then filtered. The solvent is removed to leave the desired product as a colorless oil which needed no further purification.

(3S)-3-Hydroxymethylpyrrolidine (8c): The amine (1.85 g, 9.01 mmol), Pd-C (10 %) (185 mg) in methanol (25 mL) is placed under a hydrogen atmosphere (50 psi) for 72 h. The product is filtered over celite with the aid of methanol (50 mL) and then the resulting solution is concentrated to afford the desired amine as a light yellow oil. No further purification is performed.

(3S)-3-Hydroxymethyl-1-[(4-methoxyphenyl)sulfonyl]pyrrolidine (8d): The 3(S)-hydroxymethylpyrrolidine (0.9 g, 8.90 mmol), triethylamine (1.80 g, 17.8 mmol, 2.0 equiv) in 1,4-dioxane (30 mL) and water (10 mL) is stirred at room temperature and then 4-methoxyphenylsulfonyl chloride (2.02 g, 9.80 mmol, 1.10 equiv) is added. The resulting solution is stirred at room temperature for 3 h. and then the solution is acidified to pH ~1 with 1 N HCl. The solution is poured into water and then extracted with CH₂Cl₂. The organic extracts are dried (Na₂SO₄) and concentrated to an oil. The oil is purified by chromatography using 1/1 hexane/EtOAc as the eluent to afford the desired product as a colorless oil.

(3S)-3-Acetylthiomethyl-1-[(4-methoxyphenyl)sulfonyl]pyrrolidine (8e): The alcohol (0.8 g, 2.95 mmol) in CH₂Cl₂ (20 mL) is added to a solution of triphenylphosphine (0.93 g, 3.54 mmol, 1.2 equiv) and diethylazodicarboxylate (0.57 g, 3.24 mmol, 1.1 equiv) in CH₂Cl₂ (20 mL) at room temperature. The solution is stirred 15 minutes at room temperature and then the thiolacetic acid (0.45 g, 5.90 mmol, 2.0 equiv) is added. The resulting solution is stirred at room temperature for 2 h. The reaction mixture is concentrated to an oil and then silica gel (20 g) is added. The resulting powder is purified by chromatography on silica gel using 8/2 hexane/EtOAc as the eluent to afford the desired thiolacetate as a clear colorless oil.

(3S)-3-Thiomethyl-1-[(4-methoxyphenyl)sulfonyl]pyrrolidine (8f): The thiolacetate (0.45 g, 1.37 mmol) in methanol (30 mL) is stirred under an argon atmosphere at room temperature. The solution is then bubbled with ammonia gas for 20 minutes at room temperature and then the solution is purged with argon gas. The solvent is removed under reduced pressure to leave a colorless oil. Purification of the oil is accomplished by chromatography using 8/2 hexane/EtOAc as the eluent. The product is obtained as a colorless oil. MS (electron spray): 288 (M + H⁺).

EXAMPLE 9**Synthesis of 2-(1-Thiol-1-(2-thiazolyl)methyl)-1-[(4-methoxyphenyl)sulfonyl]piperidine**

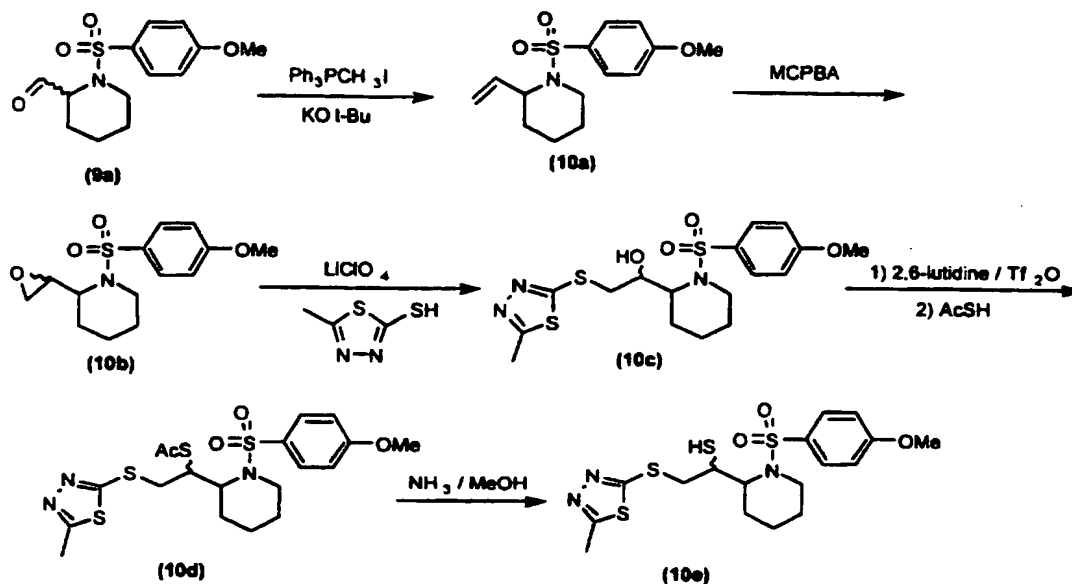
2-(*R,S*)-1-[(4-methoxyphenyl)sulfonyl]piperidinemethanal (9a): The 2-(*R,S*)-1-[(4-Methoxyphenyl)sulfonyl]piperidinemethanol (16.5 g, 57.9 mmol) is dissolved in 400 mL of dichloromethane at room temperature, followed by the addition of PDC (32.67 g, 86.8 mmol, 15 equiv). The reaction is stirred at room temperature overnight. In the morning, another 0.5 equivalents of PDC is added and the reaction mixture is stirred for an additional 4 hours. The reaction is diluted with ether and passed through a short plug silica gel column with CH₂Cl₂ as eluent to eliminate the color providing the pure product. **CI⁺ MS:** *m/z* (rel intensity) 284.0 (*M*⁺ + *H*, 100).

2-[1-Hydroxy-1-(2-thiazolyl)methyl]-1-[(4-methoxyphenyl)sulfonyl]piperidine (9b): Thiazole (0.576 mL, 8.13 mmol) is dissolved in 150 mL of THF and cooled to -78 °C in a dry ice acetone bath. *N*-butyllithium (5.0 mL, 8.13 mmol) is added slowly and this solution stirred for 30 minutes. Next, the aldehyde (2.0 g, 7.07 mmol) is dissolved in 15 mL of THF and cannulated into the solution at -78 °C. The resulting solution is stirred at -78 °C for 1 hour and at room temperature for 2 hours. The reaction is quenched with 1N HCl and extracted with ethyl acetate 3 times, the organic layer is washed with saturated sodium chloride and dried over magnesium sulfate and evaporated down. Chromatography is performed on silica gel using ethyl acetate/ hexane (1/ 1.5) to give the pure compound. **CI⁺ MS:** *m/z* (rel intensity) 397.0 (*M*⁺ + *H*, 100).

2-[1-Thioacetyl-1-(2-thiazolyl)methyl]-1-[(4-methoxyphenyl)sulfonyl]piperidine (9c): In flask 1, the azeotropically dried alcohol (0.270 g, 0.73 mmol) is dissolved in 20 mL of anhydrous methylene chloride, followed by the addition of 2,6-lutidine (0.126 mL, 1.08 mmol) and the reaction is cooled to -78 °C in a dry ice/ acetone bath. Then, the trifluoromethanesulfonic anhydride (0.135 mL, 0.80 mmol) is added and the mixture stirred at -78 °C for 45 minutes, then at 0 °C for five minutes. In a separate flask (flask 2), the

thi lacetic acid (0.174 mL, 2.44 mmol) and 2,6-lutidine (0.28 mL, 2.44 mmol) are dissolved in 10 mL of anhydrous methylene chloride. Flask 2 is cannulated into flask 1 at 0 °C. The reaction then stirred at room temperature overnight. The reaction is quenched with saturated sodium bicarbonate and water, then it is extracted 3 times with ethyl acetate and washed with saturated ammonium chloride, dried over magnesium sulfate and evaporated. A silica gel column is run using hexanes/ ethyl acetate (3/ 1) to give the pure compound.

2-[1-Thiol-1-(2-thiazolyl)methyl]-1-[(4-methoxyphenyl)sulfonyl]piperidine (9d): The thiol acetate (0.100 g, 0.234 mmol) is dissolved in 8 mL of methanol and the solution is thoroughly degassed. Anhydrous ammonia gas is passed through the solution for 8 minutes and the solution stirred for an additional 15 minutes. The solution is evaporated down to a crude product which is chromatographed on silica gel with hexanes/ ethyl acetate(3/ 1) to give the pure product.

EXAMPLE 10**Synthesis of 2-[1-thiol-2-(5-methyl-1,3,4-thiadiazol-2-yl)thio]ethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine**

2-Ethenyl-1-[(4-methoxyphenyl)sulfonyl]piperidine (10a): Triphenylphosphinemethyl iodide (22.5 g, 55.6 mmol) is suspended in 400 mL of THF and cooled to 0 °C in an ice bath and potassium *t*-butoxide (8.33 g, 74.2 mmol) is added and the reaction mixture is stirred for 1 hour. This produced a suspension of yellow solid in yellow solution. The aldehyde **9a** (10.5 g, 37.1 mmol) is dissolved in 40 mL of THF and then added to the reaction mixture. The reaction stirred at 0 °C for 4 hours. The reaction is quenched with 1N HCl and water. This is extracted with ethyl acetate 3 times and the organic layers are washed with saturated sodium bicarbonate and ammonium chloride, dried over magnesium sulfate, and evaporated to provide the product. Chromatography is performed on silica gel using hexanes/ ethyl acetate (3/ 1) to give the pure compound. Cl^+ MS: m/z (rel intensity) 331.9 ($\text{M}^+ + \text{H}$, 100).

2-Ethylene oxide-1-[(4-methoxyphenyl)sulfonyl]piperidine (10b): The alkene (4.5 g, 16.0 mmol) is dissolved in 200 mL of dichloromethane followed by the addition of MCPBA (50-75% pure) (17 g, 64 mmol). The reaction mixture is stirred at room temperature for 26 hours. The reaction is quenched with sodium sulfite (10.1g, 64.0 mmol) in water and diluted with saturated sodium bicarbonate. This is extracted with ethyl acetate 3 times and the organic layers are washed with 1N HCl, sodium bicarbonate, and ammonium chloride, dried over magnesium sulfate and evaporated down. Chromatography is

performed on silica gel using hexanes/ ethyl acetate/ methylene chloride (11/ 3/ 3) to give two different diastereomers as single pure compounds. Cl^+ MS: (rel intensity) 298 ($M^+ + H$, 100)

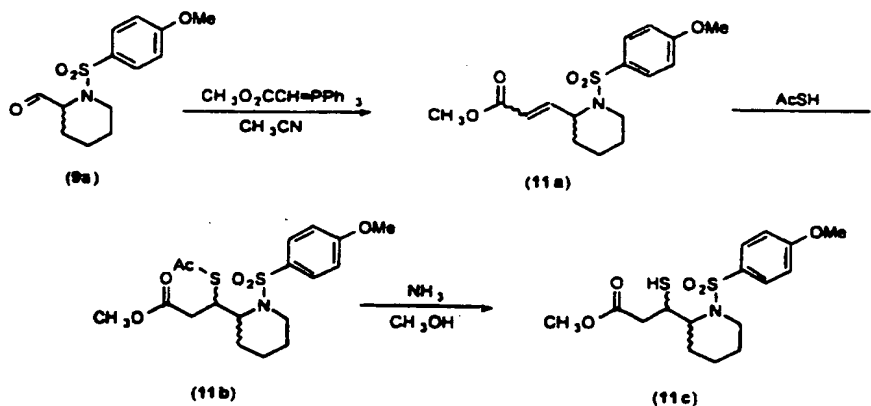
2-(1-Hydroxy-2-(5-methyl-1,3,4-thiadiazol-2-yl)thio)ethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine (10c): The more polar epoxide (0.270 g, 0.908 mmol) is dissolved in 10 mL of dichloromethane and cooled to 0 °C followed by the addition of lithium perchlorate (0.363 mL, 1.81 mmol). This mixture is stirred for 5 minutes then the 5-methyl-1,3,4-thiadiazole-2-thiol (0.480 g, 3.63 mmol) is added. The reaction mixture is stirred from 0 °C to room temperature overnight. The reaction is quenched with 1N HCl and extracted with ethyl acetate 3 times. The organic layers are washed with ammonium chloride, dried over magnesium sulfate and evaporated down. Chromatography is performed silica gel using hexanes/ ethyl acetate (1/ 1.5) to give the pure compound. Cl^+ MS: m/z (rel intensity) 430 ($M^+ + H$, 70).

2-(1-Acetylthio-2-(5-methyl-1,3,4-thiadiazol-2-yl)thio)ethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine (10d): In flask 1, the azeotropically dried alcohol (0.300g, 0.698 mmol) is dissolved in 10 mL of anhydrous methylene chloride, followed by the addition of 2,6-lutidine (0.122 mL, 1.04 mmol) and the reaction is cooled down to -78 °C in a dry ice / acetone bath. Then, the trifluoromethanesulfonic anhydride (0.129 mL, 0.768 mmol) is added and the mixture stirred at -78 °C for 45 minutes, then at 0 °C for five minutes. In a separate flask (flask 2), the thiol acetic acid (0.498 mL, 6.93 mmol) and 2,6-lutidine (0.81 mL, 6.93 mmol) are dissolved in 10 mL of anhydrous methylene chloride. Flask 2 is cannulated into flask 1 at 0 °C. The reaction then stirred at room temperature overnight. The reaction is quenched with saturated sodium bicarbonate and water, then it is extracted 3 times with ethyl acetate and washed with saturated ammonium chloride, dried over magnesium sulfate and evaporated. A silica gel column is run using hexanes/ ethyl acetate (1/ 2.5) to give the pure compound. Cl^+ MS: m/z (rel intensity) ($M^+ + H$, 100).

2-(1-Thiol-2-(5-methyl-1,3,4-thiadiazol-2-yl)thio)ethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine (10e): The thiol acetate (0.050 g, 0.102 mmol) is dissolved in 5 mL of methanol and the solution is thoroughly degassed. Anhydrous ammonia gas is passed through the solution for 2 minutes and the solution stirred for an additional 5 minutes. The solution is evaporated under reduced pressure to leave a crude product which is chromatographed on silica gel with hexanes/ ethyl acetate (1/ 2) to give the desired thiol. Cl^+ MS: m/z (rel intensity) ($M^+ + H$, 100).

EXAMPLE 11

Synthesis of 2-(*R,S*)-(2-methoxycarbonyl-1-(*R,S*)-mercapto)ethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine



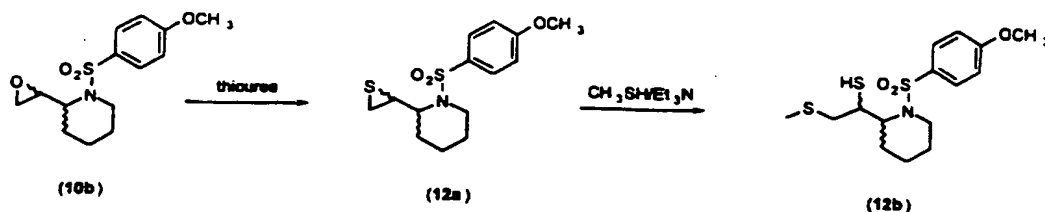
2-(2-Methoxycarbonyl)ethenyl-1-[(4-methoxyphenyl)sulfonyl]piperidine 11a: The aldehyde (450 mg, 1.59 mmol) is dissolved in 20 mL of acetonitrile. Methyl (triphenylphosphoranylidene)acetate (1.06 g, 3.18 mmol) is added. The solution is warmed to reflux and stirred for 20 hours. After cooling to room temperature, the solvent is removed by rotary evaporation. Chromatography is performed on silica gel using hexanes/ ethyl acetate (2/ 1) to give pure compound. CI^+MS : m/z (rel intensity) 340 ($\text{M}^+ + \text{H}$, 53).

2-(*R,S*)-(2-Methoxycarbonyl-1-(*R,S*)-thiacetyl)ethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine 11b: The α,β -unsaturated ester (462 mg, 1.36 mmol) is dissolved in 25 mL of thioacetic acid. The solution is warmed to 80°C and stirred for 5 days. After cooling to room temperature, the solvent is removed by rotary evaporation. Chromatography is performed on silica gel using methanol/ dichloromethane (3%) to give pure compound. CI^+MS : m/z (rel intensity) 416 ($\text{M}^+ + \text{H}$, 100).

2-(*R,S*)-(2-Methoxycarbonyl-1-(*R,S*)-mercapto)ethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine 11c: The thiolacetate is dissolved in 25 mL of methanol and the solution degassed with argon for 20 minutes. The solution is cooled to -50°C and ammonia is bubbled in at such a rate as to keep the temperature below -20°C . When the addition of ammonia is no longer exothermic, the flow is stopped and the mixture is stirred under argon at -60°C for 1 hour. The mixture is warmed to room temperature and the solvent removed by rotary evaporation. Chromatography is performed on silica gel using methanol/ dichloromethane (0.5%) to give pure compounds as separable diastereomers. CI^+MS : m/z (rel intensity) 374 ($\text{M}^+ + \text{H}$, 65).

EXAMPLE 12

Synthesis of 2-(*R,S*)-(2-methylthio-1-(*R,S*)-mercapt)ethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine

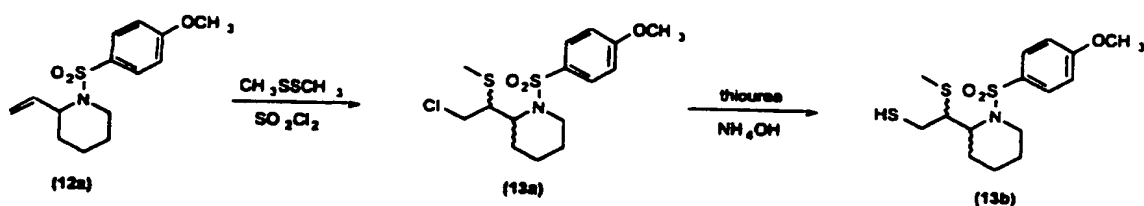


2-(*R,S*)-(2-ethylene sulfide)-1-[(4-methoxyphenyl)sulfonyl]piperidine 12a: The epoxide (0.124 mg, 0.415 mmol) is dissolved in 3.7 mL of methanol under argon. Thiourea (63.3 mg, 0.831 mmol) is added and the mixture stirred for 7 days. The solvent was removed by rotary evaporation. Chromatography is performed on silica gel using hexanes/ ethyl acetate (2/ 1) to give pure compound. FAB⁺MS: *m/z* (rel intensity) 374 (*M*⁺ +H, 23).

2-(*R,S*)-(2-methylthio-1-(*R,S*)-mercapto)ethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine 12b: The episulfide (25.7 mg, 0.0798 mmol) is dissolved in 4 mL of DMF under argon. Triethylamine (53 mL, 0.383 mmol) is added and the mixture is cooled to -55°C. Methyl mercaptan is passed through the solution for 15 minutes and the mixture stirred at -55°C for 4 hours. The bath is removed and the mixture stirred at room temperature for 16 hours. The solvent is removed by rotary evaporation. The crude product is purified by radial chromatography using hexanes/ ethyl acetate (6/ 1). ion spray MS: *m/z* (rel intensity) 362 (*M*⁺ +H, 42).

EXAMPLE 13

Synthesis of 2-(*R,S*)-(1-(*R,S*)-methylthio-2-mercapto)ethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine

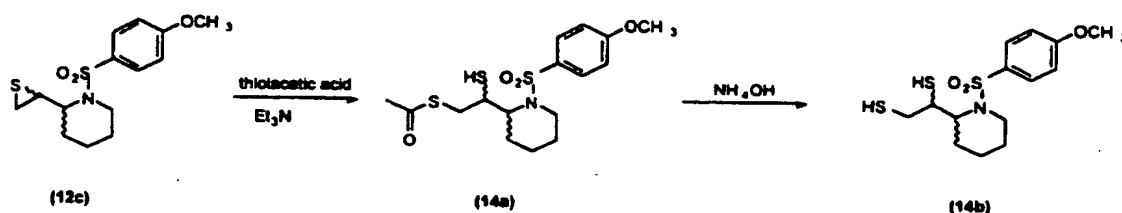


2-(*R,S*)-(1-(*R,S*)-methylthio-2-chloro)ethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine 13a: Methyl disulfide (32 mL, 0.355 mmol) is dissolved in 5 mL of 1,2-dichloroethane and cooled to -40°C. Sulfuryl chloride (29 mL, 0.355 mmol) is added via syringe. The mixture is warmed -10°C and cooled to -40°C. A solution of the alkene in 1 mL of 1,2-dichloroethane is added via syringe. The cold bath is removed and the mixture stirred at room temperature for 16 hours. The solvent is removed by rotary evaporation. Chromatography is performed on silica gel using hexanes/ ethyl acetate (4/ 1) to give pure compound. CI⁺MS: *m/z* (rel intensity) 364 (*M*⁺ +H, 100).

2-(*R,S*)-(1-(*R,S*)-methylthio-2-mercapto)ethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine 13b: The chlorosulfide (50.0 mg, 0.137 mmol) is dissolved in 5 mL of 95% ethanol. Thiourea (12.6 mg, 0.165 mmol) is added and the mixture warmed to reflux temperature for 4 hours. After cooling to room temperature, the solvent is removed by rotary evaporation. The residue is treated with 5 mL of concentrated ammonium hydroxide at 85°C for 1 hour. The mixture is cooled to room temperature, diluted with water, and extracted with two portions of ethyl acetate. The combined organic layers are washed three times with water, dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation. The crude product is purified by radial chromatography using hexanes/ ethyl acetate (4/ 1). ion spray MS: m/z (rel intensity) 362 ($M^+ + H$, 100).

EXAMPLE 14

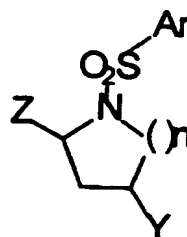
Synthesis of 2-(*R,S*)-(1-(*R,S*)-2-dithio)ethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine



2-(*R,S*)-(2-thioacetyl-1-(*R,S*)-mercapto)ethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine 14a: The episulfide (25 mg, 0.0798 mmol) is dissolved in 2 mL of ethyl acetate. Triethylamine (40 mL, 0.287 mmol) and thiolacetic acid (25 mL, 0.251 mmol) are added and the mixture stirred for 16 hours at room temperature and 4.5 hours at 50°C. The reaction mixture is diluted with ethyl acetate and washed with three portions of 5% NaHCO_3 . The organic layer is dried over Na_2SO_4 , filtered, and the solvent removed by rotary evaporation. The crude product is purified by radial chromatography using hexanes/ ethyl acetate (4/ 1).

2-(*R,S*)-(1-(*R,S*)-2-dithio)ethyl-1-[(4-methoxyphenyl)sulfonyl]piperidine 14b: The thiolacetate is dissolved in 25 mL of methanol and the solution degassed with argon for 20 minutes. The solution is cooled to -50°C and ammonia is bubbled in at such a rate as to keep the temperature below -20°C. When the addition of ammonia is no longer exothermic, the flow is stopped and the mixture is stirred under argon at -60°C for 1 hour. The mixture is warmed to room temperature and the solvent removed by rotary evaporation. The crude product is purified by radial chromatography using methanol/ dichloromethane (0.5%). ion spray⁺MS: m/z (rel intensity) 348 ($M^+ + H$, 100).

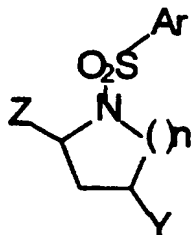
The following compounds are made using the methods described and exemplified above. For the purpose of illustration, Y is shown as R2 and Z is shown as R1



| | Z | Y | (n) | Ar |
|------------|---|---|-----|--------------------------------------|
| Example 15 | -CH ₂ SH | -OH | 1 | 4-MeOC ₆ H ₄ - |
| Example 16 | -CH ₂ SH | -SC ₆ H ₄ OMe | 1 | 4-MeOC ₆ H ₄ - |
| Example 17 | H | SH | 2 | 4-MeOC ₆ H ₄ - |
| Example 18 | MeO ₂ CCH ₂ CH(SH)- | OH | 1 | 4-MeOC ₆ H ₄ - |
| Example 19 | MeO ₂ CCH ₂ CH(SH)- | SH | 1 | 4-MeOC ₆ H ₄ - |
| Example 20 | MeO ₂ CCH ₂ CH(SH)CH ₂ - | H | 2 | 4-MeOC ₆ H ₄ - |
| Example 21 | <i>t</i> -BuO ₂ CCH ₂ CH(SH)- | H | 2 | 4-MeOC ₆ H ₄ - |
| Example 22 | HO ₂ CCH ₂ CH(SH)- | H | 2 | 4-MeOC ₆ H ₄ - |
| Example 23 | MeSCH ₂ CH(SMe)- | H | 2 | 4-MeOC ₆ H ₄ - |
| Example 24 | (N-morpholinyl)- (CH ₂) ₂ NHCOCH ₂ CH(SH)- | H | 2 | 4-MeOC ₆ H ₄ - |
| Example 25 | MeO ₂ CCH ₂ CH(SH)- | -OCH ₂ CH ₂ O- | 1 | C ₆ H ₅ - |
| Example 26 | MeO ₂ CCH ₂ CH(SH)- | -SCH ₂ CH ₂ S- | 1 | 4-MeOC ₆ H ₄ - |
| Example 27 | MeO ₂ CCH ₂ CH(SH)- | -SCH ₂ CH ₂ CH ₂ S- | 1 | 4-MeOC ₆ H ₄ - |
| Example 28 | HSCH ₂ | OH | 1 | n-HEXYL |
| Example 29 | HSCH ₂ CH(SMe)- | OMe | 1 | n-BUTYL |
| Example 30 | MeSCH ₂ CH(SMe)- | (2-benzathiazole) | 2 | 2-PYRIDYL |
| Example 31 | HSCH ₂ | (2-imidazole) | 2 | 4-MeOC ₆ H ₄ - |
| Example 32 | PhSCH ₂ | OPh | 3 | 4-MeOC ₆ H ₄ - |
| Example 33 | HSCH ₂ | HO(C ₆ H ₄)OCH ₂ Ph | 1 | 4-MeOC ₆ H ₄ - |
| Example 34 | HSCH ₂ | O(2-(C ₆ H ₄)NHPh) | 2 | 4-MeOC ₆ H ₄ - |
| Example 35 | HSCH ₂ | OXY(2-PYRIDYL) | 1 | 2-PYRIDYL |
| Example 36 | PhSCH ₂ | SPh | 2 | 4-MeOC ₆ H ₄ - |
| Example 37 | HSCH ₂ | S(4-C ₆ H ₄ OMe) | 2 | 4-MeOC ₆ H ₄ - |
| Example 38 | HSCH ₂ | SPh | 2 | 4-MeOC ₆ H ₄ - |
| Example 39 | MeO ₂ CCH ₂ CH(SH)CH ₂ - | H | 2 | 4-MeOC ₆ H ₄ - |
| Example 40 | HSCH ₂ | NH(CH ₂) ₅ CH ₃ | 2 | 4-MeOC ₆ H ₄ - |

Me=methyl, Ph=phenyl; C₆H₄=phenyl diradical

The following compounds are made using the methods described and exemplified above. All compounds exemplified below have Z (or R₁) as MeO₂CCH₂CH(SH)-



| | Y | Ar | n |
|------------|---|---|---|
| Example 41 | -NHCO(pyridyl) | -C ₆ H ₄ OCH ₃ | 1 |
| Example 42 | -NHCOCH ₃ | -C ₆ H ₄ OCH ₃ | 1 |
| Example 43 | -NHCOCH ₂ C ₆ H ₅ | -C ₆ H ₄ OCH ₃ | 1 |
| Example 44 | -NHSO ₂ NHCH ₂ CH ₃ | -C ₆ H ₄ OCH ₃ | 1 |
| Example 45 | -NHSO ₂ NH ₂ | -C ₆ H ₄ OCH ₃ | 1 |
| Example 46 | -NHSO ₂ N(CH ₃) ₂ | -C ₆ H ₄ OCH ₃ | 1 |
| Example 47 | -NHSO ₂ CH ₃ | -C ₆ H ₄ OCH ₃ | 1 |
| Example 48 | -NHSO ₂ C ₆ H ₄ OCH ₃ | -C ₆ H ₄ OCH ₃ | 1 |
| Example 49 | -NHP(O)(CH ₃)C ₆ H ₅ | -C ₆ H ₄ OCH ₃ | 1 |
| Example 50 | -N(CH ₃)COC ₆ H ₅ | -C ₆ H ₄ OCH ₃ | 1 |
| Example 51 | -N(CH ₃)(CH ₂ CH ₂ CH ₃) | -C ₆ H ₄ OCH ₃ | 1 |
| Example 52 | -N(CH ₂ CH ₂ CH ₃) ₂ | -C ₆ H ₄ OCH ₃ | 1 |
| Example 53 | -N(CH ₂ CH ₃)SO ₂ CH ₃ | -C ₆ H ₄ OCH ₃ | 1 |
| Example 54 | -CH ₂ NHSO ₂ CH ₃ | -C ₆ H ₄ OCH ₃ | 1 |
| Example 55 | -CH ₂ NH SO ₂ C ₆ H ₅ | -C ₆ H ₄ OCH ₃ | 1 |
| Example 56 | -CH ₂ NHCOC ₆ H ₅ | -C ₆ H ₄ OCH ₃ | 1 |
| Example 57 | -CH ₂ NHCOCH ₂ CH ₂ CH ₃ | -C ₆ H ₄ NO ₂ | 1 |
| Example 58 | -CH ₂ N(CH ₃)COCH ₃ | -C ₆ H ₄ Br | 1 |
| Example 59 | -CH ₂ N(CH ₃)SO ₂ C ₆ H ₅ OMe | -C ₆ H ₄ Br | 1 |
| Example 60 | -CH ₂ N(CH ₂ C ₆ H ₅)SO ₂ CH ₃ | -C ₆ H ₄ Br | 1 |
| Example 61 | -OH | -C ₆ H ₄ OCH ₃ | 2 |
| Example 62 | -S-C ₆ H ₅ | -C ₆ H ₄ OCH ₃ | 2 |
| Example 63 | -H | -C ₆ H ₄ OCH ₃ | 2 |

| | | | |
|------------|---|---|---|
| Example 64 | -OH | -C ₆ H ₄ OCH ₃ | 1 |
| Example 65 | -(OH)[CH(CH ₃) ₂] | -C ₆ H ₄ OCH ₃ | 1 |
| Example 66 | -(OH)(C ₆ H ₅) | -C ₆ H ₄ OCH ₃ | 1 |
| Example 67 | -(OH)(2-thiophenyl) | -C ₆ H ₄ OCH ₃ | 1 |

These examples provide the skilled artisan with sufficient guidance as to making the present invention and do not limit it in any way.

Composition and Method of Use Examples

The compounds of the invention are useful to prepare compositions for the treatment of ailments and the like. The following composition and method examples do not limit the invention, but provide guidance to the skilled artisan to prepare and use the compounds, compositions and methods of the invention. In each case the compounds formula I may be substituted for the example compound shown below with similar results.

The methods of use exemplified do not limit the invention, but provide guidance to the skilled artisan to use the compounds, compositions and methods of the invention. The skilled practitioner will appreciate that the examples provide guidance and may be varied based on condition and the patient.

Example A

A tablet composition for oral administration, according to the present invention, is made comprising:

| <u>Component</u> | <u>Amount</u> |
|--------------------|---------------|
| Example 9 | 15. mg |
| Lactose | 120. mg |
| Maize Starch | 70. mg |
| Talc | 4. mg |
| Magnesium Stearate | 1. mg |

Other compounds having a structure according to Formula (I) are used with substantially similar results.

A human female subject weighing 60 kg (132 lbs), suffering from rheumatoid arthritis, is treated by a method of this invention. Specifically, for 2 years, a regimen of three tablets per day is administered orally to said subject.

At the end of the treatment period, the patient is examined and is found to have reduced inflammation, and improved mobility without concomitant pain.

Example B

A capsule for oral administration, according to the present invention, is made comprising:

| <u>Component</u> | <u>Amount (%w/w)</u> |
|---------------------|----------------------|
| Example 3 | 15% |
| Polyethylene glycol | 85% |

Other compounds having a structure according to Formula (I) are used with substantially similar results.

A human male subject weighing 90 kg (198 lbs), suffering from osteoarthritis, is treated by a method of this invention. Specifically, for 5 years, a capsule containing 70 mg of Example 3 is administered daily to said subject.

At the end of the treatment period, the patient is examined via orthoscopy, and found to have no further advancement of erosion/fibrillation of the articular cartilage.

Example C

A saline-based composition for local administration, according to the present invention, is made comprising:

| <u>Component</u> | <u>Amount (%w/w)</u> |
|-------------------|----------------------|
| Example 13 | 5 % |
| Polyvinyl alcohol | 15% |
| Saline | 80% |

Other compounds having a structure according to Formula (I) are used with substantially similar results.

A patient having deep corneal abrasion applies the drop to each eye twice a day. Healing is speeded, with no visual sequelae.

Example D

An topical composition for local administration, according to the present invention, is made comprising:

| <u>Component</u> | <u>Composition (% w/v)</u> |
|-----------------------|----------------------------|
| Compound of Example 3 | 0.20 |
| Benzalkonium chloride | 0.02 |
| Thimerosal | 0.002 |
| d-Sorbitol | 5.00 |
| Glycine | 0.35 |
| Aromatics | 0.075 |
| Purified water | <u>q.s.</u> |
| Total = | 100.00 |
| Total = | 100.00 |

Any of the other compounds having a structure according to Formula (I) are used with substantially similar results.

A patient suffering from chemical burns applies the composition at each dressing change (b.i.d.). Scarring is substantially diminished.

Example E

A inhalation aerosol composition, according to the present invention, is made comprising:

| <u>Component</u> | <u>Composition (% w/v)</u> |
|-----------------------|----------------------------|
| Compound of Example 2 | 5.0 |

| | |
|------------------------|-------------|
| Alcohol | 33.0 |
| Ascorbic acid | 0.1 |
| Menthol | 0.1 |
| Sodium Saccharin | 0.2 |
| Propellant (F12, F114) | <u>q.s.</u> |
| Total = | 100.0 |

Any of the other compounds having a structure according to Formula (I) are used with substantially similar results.

An asthma sufferer sprays 0.01 mL via a pump actuator into the mouth while inhaling. Asthma symptoms are diminished.

Example F

A topical ophthalmic composition, according to the present invention, is made comprising:

| <u>Component</u> | <u>Composition (% w/v)</u> |
|-------------------------------------|----------------------------|
| Compound of Example 5 | 0.10 |
| Benzalkonium chloride | 0.01 |
| EDTA | 0.05 |
| Hydroxyethylcellulose (NATROSOL M™) | 0.50 |
| Sodium metabisulfite | 0.10 |
| Sodium chloride (0.9%) | <u>q.s.</u> |
| Total = | 100.0 |

Any of the other compounds having a structure according to Formula (I) are used with substantially similar results.

A human male subject weighing 90 kg (198 lbs), suffering from corneal ulcerations, is treated by a method of this invention. Specifically, for 2 months, a saline solution containing 10 mg of Example 5 is administered to said subject's affected eye twice-daily.

Example G

A composition for parenteral administration is made comprising:

| <u>Component</u> | <u>Amount</u> |
|---|-------------------|
| Example 4 | 100 mg/ml carrier |
| <u>Carrier:</u> | |
| sodium citrate buffer with (percent by weight of carrier): | |
| lecithin | 0.48% |
| carboxymethylcellulose | 0.53 |
| povidone | 0.50 |

| | |
|----------------|-------|
| methyl paraben | 0.11 |
| propyl paraben | 0.011 |

The above ingredients are mixed, forming a suspension. Approximately 2.0 ml of the suspension is administered, via injection, to a human subject with a premetastatic tumor. The injection site juxtaposes the tumor. This dosage is repeated twice daily, for approximately 30 days. After 30 days, symptoms of the disease subside, and dosage is gradually decreased to maintain the patient.

Other compounds having a structure according to Formula I are used with substantially similar results.

Example H

A mouthwash composition is prepared;

| <u>Component</u> | <u>%w/v</u> |
|------------------|-----------------|
| Example 1 | 3.00 |
| SDA 40 Alcohol | 8.00 |
| Flavor | 0.08 |
| Emulsifier | 0.08 |
| Sodium Fluoride | 0.05 |
| Glycerin 10.00 | |
| Sweetener | 0.02 |
| Benzoic acid | 0.05 |
| Sodium hydroxide | 0.20 |
| Dye | 0.04 |
| Water | balance to 100% |

A patient with gum disease uses 1 ml of the mouthwash thrice daily to prevent further oral degeneration.

Other compounds having a structure according to Formula I are used with substantially similar results.

Example I

A lozenge composition is prepared;

| <u>Component</u> | <u>%w/v</u> |
|------------------|-----------------|
| Example 3 | 0.01 |
| Sorbitol | 17.50 |
| Mannitol | 17.50 |
| Starch | 13.60 |
| Sweetener | 1.20 |
| Flavor | 11.70 |
| Color | 0.10 |
| Corn Syrup | balance to 100% |

A patient uses the lozenge to prevent loosening of an implant in the maxilla. . . Other compounds having a structure according to Formula I are used with substantially similar results.

Example J

Chewing Gum Composition

| <u>Component</u> | <u>w/v%</u> |
|---------------------------------|-------------|
| Example 1 | 0.03 |
| Sorbitol crystals | 38.44 |
| Paloja-T gum base* | 20.00 |
| Sorbitol (70% aqueous solution) | 22.00 |
| Mannitol | 10.00 |
| Glycerine | 7.56 |
| Flavor | 1.00 |

A patient chews the gum to prevent loosening to prevent loosening of dentures.

Other compounds having a structure according to Formula I are used with substantially similar results.

Example K

| <u>Components</u> | <u>w/v%</u> |
|-------------------|-------------|
| USP Water | 54.656 |
| Methylparaben | 0.05 |
| Propylparaben | 0.01 |
| Xanthan Gum | 0.12 |
| Guar Gum | 0.09 |
| Calcium carbonate | 12.38 |
| Antifoam | 1.27 |
| Sucrose | 15.0 |

| | |
|----------------|---------|
| Sorbitol | 11.0 |
| Glycerin | 5.0 |
| Benzyl Alcohol | 0.2 |
| Citric Acid | 0.15 |
| Coolant | 0.00888 |
| Flavor | 0.0645 |
| Colorant | 0.0014 |

Example 1 is prepared by first mixing 80 kg of glycerin and all of the benzyl alcohol and heating to 65 C, then slowly adding and mixing together methylparaben, propylparaben, water, xanthan gum, and guar gum. Mix these ingredients for about 12 minutes with a Silverson in-line mixer. Then slowly add in the following ingredients in the following order: remaining glycerin, sorbitol, antifoam C, calcium carbonate, citric acid, and sucrose. Separately combine flavors and coolants and then slowly add to the other ingredients. Mix for about 40 minutes.

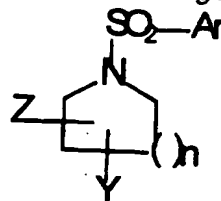
The patient takes the formulation to prevent flare up of colitis.

All references described herein are hereby incorporated by reference.

While particular embodiments of the subject invention have been described, it will be obvious to those skilled in the art that various changes and modifications of the subject invention can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of this invention.

WHAT IS CLAIMED IS:

1. A compound having the structure according to Formula I,



(I)

wherein

n is an integer from 1 to 3, and 0 to 2 additional heteroatoms, chosen from O, N, or S may occur in the backbone of the ring in the place of carbon, and where S occurs it may be in the form S, SO, or SO_2 and where N occurs it is in the form NR_5 and R_5 is chosen from hydrogen, alkyl, heteroalkyl, heteroaryl, aryl, SO_2R_{10} , COR_{11} , CSR_{12} , $\text{PO}(\text{R}_{13})_2$;

Z is independently one or more of $(\text{CH}_2)_m(\text{CR}_1\text{R}_2)_o\text{SR}_3$; and

R_1 is independently hydrogen, alkyl, CH_2SR_3 or $\text{CH}_2\text{C}(\text{W})\text{R}_4$, and R_4 is alkoxy, hydroxy, NR_5 , alkylthio, or thio; and R_5 is independently one or more of heterocyclalkyl, alkyl, aryl, heteroalkyl, heteroaryl, hydrogen, or together with W, may form a heterocyclic ring;

R_2 is hydrogen, alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylene, aryl or heteroaryl,

W is O or S,

R_3 is hydrogen, alkyl, aryl, heteroaryl;

and m and o are integers, independently chosen from 0, 1 and 2;

Y is independently one or more of hydrogen, hydroxy, oxo, a spiro moiety, SOR_6 , SO_2R_{10} , alkoxy, aryloxy, alkyl aryl, heteroaryl, COR_{11} , CSR_{12} , amino, wherein amino is of formula NR_8R_9 , wherein R_8 and R_9 are independently chosen from hydrogen, alkyl, heteroalkyl, heteroaryl, aryl, OR_3 , SO_2R_{10} , COR_{11} , CSR_{12} , $\text{PO}(\text{R}_{13})_2$; and

R_6 is alkyl, aryl, heteroaryl;

R_{10} is alkyl, aryl, heteroaryl, heteroalkyl, amino, alkylamino, dialkylamino, arylamino, diarylamino and alkylaryl amino;

R_{11} is hydrogen, alkoxy, aryloxy, heteroaryloxy, alkyl, aryl, heteroaryl, heteroalkyl, amino, alkylamino, dialkylamino, arylamino and alkylaryl amino;

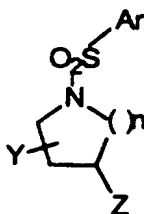
R_{12} is alkyl, aryl, heteroaryl, heteroalkyl, amino, alkylamino, dialkylamino, arylamino, diarylamino and alkylaryl amino;

R_{13} is alkyl, aryl, heteroaryl, heteroalkyl;

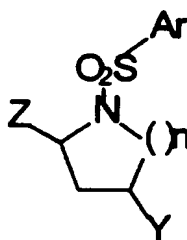
Ar is substituted or unsubstituted; alkyl, aryl, carbocyclyl, heterocyclyl, or heteroaryl; or an optical isomer, diastereomer, enantiomer, or a pharmaceutically-acceptable salt, or biohydrolyzable ester, amide, or imide thereof.

2. The compound of any preceding Claim 1, wherein Z is selected from thio, alkylthio, thioalkyl, $R_3SCH_2CH(SR_3)-$ and $R_4C(O)CH_2CH(SR_3)-$.

3. The compound of any preceding claim, of structure;



4. The compound of any preceding claim, of structure;



5. The compound of any preceding claim, wherein Ar is phenyl or substituted phenyl.

6. The compound of any preceding claim, wherein Ar is substituted phenyl and the substitution is with hydroxy, alkoxy, nitro or halo.

7. The compound of any preceding claim, wherein n is 1 or 2.

8. The compound of any preceding claim, wherein Y is one or more of hydrogen, or C_1 to C_4 alkyl.

9. The compound of any preceding claim, wherein the compound has two Z moieties chosen from thio and thiomethyl.

10. The compound of any preceding claim, wherein Z is $\text{CH}_3\text{OC(O)CH}_2\text{CH(SH)-}$; or $\text{R}_3\text{SCH}_2\text{CH(SH)-}$, and R_3 is heteroaryl.
11. The use of a compound of any preceding claim to prepare a pharmaceutical composition.
12. A method for preventing or treating a disease associated with unwanted metalloprotease activity in a mammalian subject, the method comprising administering to said subject a safe and effective amount of a compound of any preceding claim.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/14554

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D207/48 C07D211/96 A61K31/445 A61K31/40 C07D417/06
C07D417/12 C07D417/14 C07D403/04 C07D401/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | EP 0 471 236 A (TAKEDA CHEMICAL INDUSTRIES LTD) 19 February 1992 see general formula I and definitions of X and A and B, and examples 36 and 59 --- | 1,3,7,8, 11 |
| X | US 4 695 575 A (F.E.JANSENS ET AL) 22 September 1987 see general formula and definitions of L, column 2, lines 57-58 and example 21 --- | 1,3,5-8, 11 |
| X | EP 0 206 415 A (JANSSEN PHARMACEUTICA N. V.;BELG.) 30 December 1986 see general formula and definitions of L and example 13 --- | 1,3,5-8, 11 |
| | --- -/-- | |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

26 November 1997

Date of mailing of the international search report

16. 12. 97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/14554

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | EP 0 160 436 A (ROBINS, A. H., CO., INC.;USA) 6 November 1985 see formulae on pages 22-23 and chart 2 and preparation 12 --- | 1,3,5-8 |
| X | EP 0 298 818 A (ROUSSEL-UCLAF) 11 January 1989 see general formula and all examples --- | 1,2,4-8, 11 |
| X | US 3 501 489 A (P.H.L.WEI ET AL) 17 March 1970 see formula A and example VIII --- | 1,4-8,11 |
| P,X | IIDA T ET AL: "New Asymmetric Reactions Using a Gallium Complex: A Highly Enantioselective Ring Opening of Epoxides with Thiols Catalyzed by a Gallium.cntdot.Lithium.cntdot.bis(binaphth oxide) Complex" J. AM. CHEM. SOC. (JACSAT,00027863);97; VOL.119 (20); PP.4783-4784, UNIVERSITY OF TOKYO;FACULTY OF PHARMACEUTICAL SCIENCES; TOKYO; 113; JAPAN (JP), XP002048146 see product 17(Table 1, entry 7) --- | 1-3,5,7, 8 |
| X | COLDHAM I ET AL: "Synthesis of cyclic amines and allylic sulfides by phenylthio migration of.beta.-hydroxy sulfides" J. CHEM. SOC., PERKIN TRANS. 1 (JCPRB4,0300922X);93; (14); PP.1637-56, UNIV. CHEM. LAB.;CAMBRIDGE; CB2 1EW; UK (GB), XP002048147 see compound 53, page 1643 --- | 1,3,5,7, 8 |
| X | KASZUBSKA J ET AL: "Synthesis of derivatives of 2-[2-(arylthio)ethyl]pyrrolidine" POL. J. CHEM. (PJCHDQ);82; VOL.56 (10-12); PP.1543-7, POLYTECH. UNIV.;INST. FUNDAM. CHEM.; SZCZECIN; 71065; POL. (PL), XP000618493 see compound 3f, Table 1 --- | 1,4,7,8 |

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/14554

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | <p>CHEMICAL ABSTRACTS, vol. 120, no. 9, 28 February 1994 Columbus, Ohio, US; abstract no. 106714, NAKAGAWA M ET AL: "Efficient Michael addition reactions of the N-(arylsulfonyl)-3-phenylthiopiperidones. Synthesis of 3-substituted dihydropyridinones" XP002048148 see compound I and RN=143076-20-4, the 4-methylphenylsulfonyl derivative of compound I see abstract & HETEROCYCLES (HTCYAM,03855414);93; VOL.35 (2); PP.1157-70, CHIBA UNIV.;FAC. PHARM. SCI.; CHIBA; 263; JAPAN (JP), ---</p> | 1,3,5,7, 8 |
| X | <p>CHEMICAL ABSTRACTS, vol. 073, no. 5, 3 August 1970 Columbus, Ohio, US; abstract no. 025845, VERBISCAR A J ET AL: "Synthesis of cis- and trans-4-mercapto-L-proline derivatives" XP002048149 RN=23967-33-1, Proline,4-mercapto-1-(p-tolylsulfonyl)-,m ethyl ester, L-cis (for the case Y is COR11 in the application) see abstract & J. ORG. CHEM. (JOCEAH);70; VOL.35 (6); PP.1924-7, INST. OF DRUG DESIGN, INC.;SIERRA MADRE; CALIF., ---</p> | 1-3,5,7, 8 |
| P,X | <p>CHEMICAL ABSTRACTS, vol. 126, no. 17, 28 April 1997 Columbus, Ohio, US; abstract no. 225294, OHTANI, MITSUAKI ET AL: "Preparation of pyrrolidine derivatives as phospholipase A2 inhibitors" XP002048150 for the compounds wherein Y is COR11, RN=188110-15-8, L-Proline, 1-({1,1'-biphenyl}-4-yl-sulfonyl)-4-(methy lthio)-methyl ester (4S)- see abstract & WO 97 05135 A (SHIONOGI AND CO., LTD., JAPAN;OHTANI, MITSUAKI; KATO, TOSHIYUKI; WATAN) --- -/--</p> | 1-3,7,8, 11 |

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/14554

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| P,Y | WO 97 20824 A (AGOURON PHARMACEUTICALS INC) 12 June 1997 see general formula 1, wherein the only difference is the NHOH and all examples --- | 1-12 |
| Y | EP 0 606 046 A (CIBA-GEIGY AG) 13 July 1994 see the definition of R and R1 --- | 1-12 |
| P,X | CHEMICAL ABSTRACTS, vol. 126, no. 21, 26 May 1997 Columbus, Ohio, US; abstract no. 277320, TANNER, DAVID ET AL: "Total synthesis of balanol. Part 2. Completion of the synthesis and investigation of the structure and reactivity of two key heterocyclic intermediates" XP002048152 RN=189013-42-1, 1H-Azepin-3-ol,4-(ethylthio)hexahydro-1-[(4-methylphenyl)sulfonyl]- see abstract & TETRAHEDRON (1997), 53(13), 4857-4868 CODEN: TETRAB;ISSN: 0040-4020, 1997, ----- | 1-3,5,6, 8 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/14554

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 97/14554

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of
-----the following reasons:

Claims Nos.: 12

because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Claims Nos.: 1-11(part)

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The claims 1-11 have only been searched in as far as the heterocycle is only N containing, i.e. that n is an integer from 1-3 without the possibility of further heteroatoms in the ring, as all examples are only N-containing

Remark : Although claim 12 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/14554

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| EP 471236 A | 19-02-92 | AT 119774 T | 15-04-95 |
| | | CA 2048110 A | 31-01-92 |
| | | DE 69108138 D | 20-04-95 |
| | | ES 2069137 T | 01-05-95 |
| | | JP 5039221 A | 19-02-93 |
| | | US 5395839 A | 07-03-95 |
| | | US 5587383 A | 24-12-96 |
| | | US 5244908 A | 14-09-93 |
| | | JP 5051383 A | 02-03-93 |
| ----- | | | |
| US 4695575 A | 22-09-87 | US 4839374 A | 13-06-89 |
| | | AU 573673 B | 16-06-88 |
| | | AU 3736485 A | 12-09-85 |
| | | BG 40965 A | 14-03-87 |
| | | CA 1259609 A | 19-09-89 |
| | | DE 3486121 A | 06-05-93 |
| | | DK 8985 A | 10-07-85 |
| | | EP 0151826 A | 21-08-85 |
| | | IE 59707 B | 23-03-94 |
| | | JP 7068240 B | 26-07-95 |
| | | JP 60185777 A | 21-09-85 |
| ----- | | | |
| EP 0206415 A | 30-12-86 | AU 588890 B | 28-09-89 |
| | | AU 5919186 A | 08-01-87 |
| | | CA 1267889 A | 17-04-90 |
| | | DE 3687601 A | 11-03-93 |
| | | DK 295286 A | 25-12-86 |
| | | IE 59658 B | 09-03-94 |
| | | JP 62000487 A | 06-01-87 |
| | | SU 1581221 A | 23-07-90 |
| | | US 5041448 A | 20-08-91 |
| | | US 5258380 A | 02-11-93 |
| ----- | | | |
| EP 0160436 A | 06-11-85 | AU 565886 B | 01-10-87 |
| | | AU 3811685 A | 17-10-85 |
| | | CA 1247093 A,C | 20-12-88 |
| | | JP 60228454 A | 13-11-85 |
| | | US 4593102 A | 03-06-86 |
| | | US 4642348 A | 10-02-87 |
| ----- | | | |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/14554

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| EP 298818 A | 11-01-89 | DE 3874030 A | 01-10-92 |
| | | ES 2051876 T | 01-07-94 |
| | | JP 1026557 A | 27-01-89 |
| | | MX 12051 A,B | 01-10-93 |
| | | US 4897414 A | 30-01-90 |
| ----- | | | |
| US 3501489 A | 17-03-70 | US 3453289 A | 01-07-69 |
| | | US 3501463 A | 17-03-70 |
| | | US 3501496 A | 17-03-70 |
| | | US 3501512 A | 17-03-70 |
| | | US 3501526 A | 17-03-70 |
| ----- | | | |
| WO 9720824 A | 12-06-97 | AU 1409197 A | 27-06-97 |
| ----- | | | |
| EP 606046 A | 13-07-94 | US 5455258 A | 03-10-95 |
| | | AT 159012 T | 15-10-97 |
| | | AU 5265593 A | 04-05-95 |
| | | CA 2112779 A | 07-07-94 |
| | | DE 69314456 D | 13-11-97 |
| | | FI 940012 A | 07-07-94 |
| | | HU 70536 A | 30-10-95 |
| | | JP 6256293 A | 13-09-94 |
| | | MX 9400276 A | 29-07-94 |
| | | NO 940038 A,B, | 07-07-94 |
| | | NZ 250517 A | 26-10-95 |
| | | US 5506242 A | 09-04-96 |
| | | US 5552419 A | 03-09-96 |
| | | US 5646167 A | 08-07-97 |
| | | US 5672615 A | 30-09-97 |
| | | ZA 9400048 A | 11-08-94 |
| ----- | | | |